Archives of Neurology and Psychiatry

VOLUME 26 SEPTEMBER, 1931 NUMBER 3

REGENERATIVE POSSIBILITIES OF THE CENTRAL NERVOUS SYSTEM*

R. W. GERARD, PH.D., M.D.
AND
ROY R. GRINKER, M.D.
CHICAGO

It has repeatedly been demonstrated that regeneration of the central nervous system in lower animals can occur. In mammals any extensive regeneration has been denied. The absence of neurilemma about the central axons has been the usual reason given for their inability to re-form even though it is now considered that this sheath in the peripheral nervous system functions, not in re-forming the axonal structure, but probably in directing its direction of growth and furnishing nutrient materials. The clinical neurologist has always been interested in the possibilities of central regeneration as an explanation for the gradual resumption of function after severe destructive lesions. The improvement of the severe lesions in the cord associated with pernicious anemia under liver therapy and those of multiple sclerosis under fever therapy seems to cast doubt on the dictum that regeneration of the central nervous system is impossible.

In 1926, Gerard and Koppanyi [1] published, in abstract form, the results of experiments concerned with the possibility of regeneration of the spinal cord after transection in new-born and embryo rats. Only the physiologic results of the experiments, which they considered positive, were reported, pending histologic study of their specimens. In 1927, Nicholas and Hooker,[2] working under similar conditions, reported negative results and criticized the earlier work for the absence of histologic evidence and the lack of identification of the animals operated on. The latter criticism was not valid as embryos had been marked by the injection of india ink. The former criticism has now been overcome. The material from the initial experiments has been studied microscopically, and new series of experiments paralleling and ampli-

* Submitted for publication, Nov. 22, 1930.

* From the Department of Physiology and the Division of Neurology, University of Chicago.

* This study was aided by a grant from the Douglas Smith Foundation for Medical Research.

1. Gerard, R. W., and Koppanyi, T.: Studies on Spinal Cord Regeneration in the Rat, Am. J. Physiol. **76**:211, 1926.

2. Nicholas, J. S., and Hooker, D.: The Effect of Injury to the Spinal Cord of Rats in Prenatal Stages, Anat. Rec. **35**:14, 1927.

fying the original ones have been carried out. Though fully confirming the earlier physiologic observations, the histologic evidence and new experiments do not justify the conclusion that a true anatomic regeneration has been demonstrated. The regenerative changes that do occur and the physiologic reorganization of the damaged animals we consider of sufficient interest, however, to warrant discussion.

METHODS

Intra-Uterine Operations.—Female rats of timed pregnancy were operated on aseptically. A midline incision was made and the gravid uterus delivered into the wound. One uterine horn was exposed at a time to insure the identification of all the embryos. A fetus was removed from the distal end of one horn for section and study of the existing stage of development of the long intraspinal tracts in order to determine which tracts could actually have been cut.

The uterus was transilluminated with a glazed white "sinus illuminator," the back of the embryo forced against the thin transparent uterine wall at a convenient point away from the placenta by gentle external manipulation, and a cut made through the uterus and embryo with a fine cataract knife. When the knife was withdrawn, the released embryo floated free in the amniotic fluid, usually with the loss of only a small drop of blood. Little amniotic fluid leaked through the stab wound, as the uterine membranes bulged through the opening and formed a valve. In the new series of experiments, an embryo on which operation was not performed was allowed to remain as a control and was identified by amputating a portion of its tail.

It is, of course, of the utmost importance to attempt to establish with certainty that a complete transection of the cord was accomplished. Unfortunately, direct visualization of the severed cord could not be obtained without killing the embryo. There are present in the embryos, however, favorable anatomic conditions in that the middorsal line is marked by a distinct dark line in the integument and the spinal cord is extremely superficial, projecting dorsally as a cylindric rod. Further aid is obtained in young embryos by transillumination, which reveals the cerebral ventricles and in certain cases even the spinal central canal; in older embryos the tough vertebral bodies anterior to the cord can be unmistakably felt resisting the knife. At operation the knife was inserted considerably lateral to the cord on the dorsal surface of the embryo, pushed in deeply and then rotated, with the cutting edge facing medially and dorsally with the point of entry as a fulcrum. The knife was thus brought out with one clean sweep, cutting in a fan-shaped sector.

A few rats were inadvertently killed by an excess of ether after the embryos had been operated on and thus afforded unprejudiced controls. Early in the series such an experimental control revealed that in about half the embryos a complete transection of the cord had been made. Later, when the operative cut was deepened, similar controls showed complete lesions in all the embryos, but in several the cut ends were dislocated, thus creating unfavorable conditions for regenerative possibilities.

Operations on New-Born Rats.—It was found that new-born rats could be operated on immediately after birth without an excessive mortality. No anesthetic was needed, nor was strict asepsis used. The point of a cataract knife was inserted in the middorsal line, the rat being held rigidly, and was thrust ventrally until the vertebral arches were encountered, ventrolaterally to the ventral vertebral border,

and finally swept through the spinal column, as in the fetal operations. The tough cartilage of the vertebral bodies served as a tactile landmark of the depth of the knife. Bleeding was limited to a large drop of blood, and closure of the wound was not necessary. Lesions were made at low cervical or midthoracic levels.

Certain phenomena were regularly observed following a successful high transection of the cord. A flush of the hind quarters below the lesion often appeared at once, followed by slight edema. Also, as the knife passed through the cord, the irregular, struggling movements were abruptly displaced by rhythmic vigorous stepping or jumping movements of the hind legs. This characteristic "release" of the lower spinal centers was not observed when partial spinal lesions were produced.

Tests for Function.—The existence of a sense of pain caudad to the lesion is easily investigated by direct pinching of the tail or hind legs, which always leads to squeals in an intact animal but to no response in one with a separated cord. Writhing of the fore legs and head is a regular response to painful stimuli of the hind quarters in the intact animal, in addition to the vigorous movements of the hind legs. In animals in which middorsal transections have recently been performed, movements of the fore legs are absent, while the hind legs go vigorously into much the same stepping reflex movements as those seen at the time of operation. Micturition may also take place.

In the animal in which complete transection has been performed, it seems improbable that the normal response of squealing and of struggling in the front quarters can ever appear following stimulation of the skin of the hind quarters, though it might conceivably occur by means of collateral conduction along other nerve paths, such as the sympathetic nervous system. In dogs with completely transected cords, Luckhardt and Carlson [3] have not infrequently found that painful stimuli caudad to the lesion will elicit a response of the forepart of the animal; the head will turn toward the hind quarters while the eyes survey the field of stimulation. It appears as if the animal were dimly aware of something happening, but at no time is there a suggestion that pain is felt.

Tactile sensation is difficult to demonstrate with certainty in the rat. A suggestive test available about two weeks after birth, however, consists in allowing the rat to hang by its fore legs from a rod; it usually assumes a semiflexed posture with the hind legs drawn up and the tail between them, slowly lowering the support until the rump hairs touch the table top. A normal rat immediately jumps down; a rat on which transection has been recently performed will not drop until it is allowed to see the table or its weight is borne on the rump.

Proprioceptive sensibility can only be indirectly surmised from the rat's motor activity when postures and coordinate movements are normal.

The vigorous reflex activity of the spinal cord in the rat makes it difficult to be certain of voluntary activity. Coordinate standing and stepping reflexes of the hind legs are common with a complete lesion in the cord, and even a marked degree of coordinate motion of the fore and hind legs in walking is possible. Such synchronous activity may be brought about by movements of the fore limbs resulting in tension of the wall of the body. Nicholas [4] also obtained evidence of the existence of proprioceptive reflex arcs bridging over a transection of a cord. Contraction of a muscle innervated from above the lesion may initiate proprioceptive

3. Luckhardt and Carlson: Personal communication to the authors.

4. Nicholas, J. S.: Progressive Cord Degeneration and Collateral Transmission of Spinal Impulses Following Section of the Spinal Cord in Albino-Rat Foetuses, Anat. Rec. **38**:24, 1928.

tive impulses which reach the cord below the lesion. Such a mechanism would make for coordinated movements of the entire animal.

Several means are available to test the more purposeful and therefore probably the least automatic movements of the lower extremities. A normal rat when hung from a bar, or when its fore legs are placed on the edge of a flat surface with its hind legs on an inclined surface leading to it, will by vigorous crawling movements of the hind legs soon place itself entirely on the bar or flat surface. A rat with a transected cord hangs, making no attempt to use its hind legs in either case. A normal rat will similarly climb a wire net cage using all four legs, while the one with a transected cord drags its hind legs passively along, even though it may walk on a flat surface with all extremities in almost normal fashion. Furthermore, a young rat placed on its back turns over by means of strong ventroflexion of its body, lateral rotation of the head with flexion of the "snout" fore leg, extension of the opposite leg and vigorous kicking of the hind legs. The animal with a transected cord can rarely turn over from this position, and its attempts lack the bowing movement of the body and the kicking of the hind legs.

Staining Methods.—Two methods of staining were used interchangeably without preference. Some material was fixed in alcohol and impregnated with Ranson's pyridine silver method; the remainder was fixed in formaldehyde and impregnated by Freeman's modification of Bielschowsky's method. No nuclear stains were used. Portions of the cord above and below the lesion from as many specimens as possible were stained to demonstrate myelin sheaths.

The entire embryo, removed at operation to determine the stage of growth of the long intraspinal tracts, was cut serially in horizontal or coronal sections, since it was unpractical to remove the cord from so small an animal. All other cords were sectioned serially, parallel to the longitudinal fissure, in their entire length. Embedding with paraffin was used.

RESULTS

Instructive Cases in the First (1925) Series.—Rat 11, an animal operated on on Nov. 11, 1925, contained eight embryos, five of which were transected. Five days later, there were three living normal young, the ones not operated on, and two embryos apparently just recently dead. One embryo revealed only a slight subcutaneous scar. The other (rat 11) had a marked acute dorsal kyphosis. After fixation this kyphosis was seen to be made up of vertebral bodies compressed together at a sharp angle, and the canal was almost obliterated. Within this almost obliterated canal only a fine strand of fibrous tissue was found connecting the ends of the cord above and below the constriction. The cord had been completely cut.

Microscopically, above and below the lesion the cord was edematous and somewhat fragmented with a conspicuous looseness of the tissue, but the normal structure and configuration were maintained. At the site of the constriction and extending for some distance in either direction there were many freshly extravasated red blood cells enmeshed in the markedly hyperplastic leptomeninges. It seemed as if no connection existed between the two ends of the cord until in two sections, apparently in the approximate center of the meningeal mass, nerve fibers forming a bridge of nerve tissue were found. These were highly argentophilic, very coarse and irregularly placed in interwinding strands, and seemed to be derived from the ends of the anterolateral tracts above and from the lateral surfaces of the cord. They were compressed together so as to simulate a thin tract, but were not so regular. No intraspinal degenerative products were found, nor were the regenerative end-bulbs of Cajal seen.

RAT 6.—This animal was operated on three weeks after birth under ether anesthesia. A laminectomy was performed in the middorsal region, and the knife was passed along the inner vertebral margins in one sweep across the cord. The section of the cord was evidently not complete, as shown by movements and sensation in the right hind leg. Incontinence was present. Two weeks later, sensation and voluntary control of the tail and right hind leg were normal but had not completely returned in the left hind leg. A week later, the animal appeared to be entirely normal.

The rat was killed on the twenty-seventh day after the operation. A deep transverse scar was found on one side of the cord, and on the other the cord was pulled into a kink by firm adhesions to the vertebral body. Serial sections revealed that the cord had suffered a lesion in the middorsal region which had caused it to become angulated. The lesion was apparently old in that no "Abbau" products were visible. The meninges were markedly thickened and bound to the cord by bands of connective tissue within which were several small cystlike spaces. The cord was completely cut in the most ventral sections and also in the most dorsal ones, the site of the lesion being represented only by connective tissue. Furthermore, the lesion in the uppermost sections was at the concavity of the angulation and in the lower section at the convexity. Opposite the lesions at these levels the central area of the cord contained normal-appearing but compressed nerve fibers apparently traversing the cord without change. At the levels in which the lesion reached its greatest extent dorsally or ventrally, abnormal nerve fibers were seen mingled with the connective tissue and around the margins of the cyst. These were coarse, heavily impregnated fibers running in irregular fashion with free nonbulbous ends. Mixed with these were some easily identified root fibers.

RATS 7 and 25.—These animals may be discussed together. One fetus of each of these litters was operated on in utero and later delivered normally with its litter mates. At birth the two animals had normal sensation and apparently normal motion of the hind quarters and were killed at once.

Rat 25 revealed a slight thickening of the leptomeninges in the middorsal region. In the cord opposite this a small oval cavity was seen, about twice the size of a central canal, free from any material. This cavity was a short distance from the lateral surface of the cord, and a fine line of thickening extended from its boundaries obliquely in both medial and lateral directions, which, on closer study, was seen to be composed of connective tissue containing a moderate number of free nerve endings.

Rat 7 showed a nick in its anterolateral funiculus. Here the fibers of the cord were merely absent, and in the space so created a small amount of connective tissue had penetrated from the adjacent, thickened pia-arachnoid.

RAT 24.—This animal was born six days after a middorsal transection had been performed by knife. For three days there were complete anesthesia and paralysis of the hind quarters, although stepping reflexes were noted. Eight days after transection some sense of pain and voluntary motion of the left hind leg had appeared. Two weeks after the operation sense of pain and awkward but coordinated voluntary movements of both hind legs were present. Five days after this further improvement had resulted, so that the animal appeared normal save for some uncertainty in the control of the hind legs below the knees. The sense of pain and tactile sense were also present. Unfortunately, the animal was eaten, and no anatomic studies were possible.

Instructive Cases in the Second (1928) Series.—A large number of operations was performed on embryo and new-born rats, but little can be gained by a detailed presentation of all. The individuals described in detail are examples of the most striking results obtained.

Rat L6s.—This animal was operated on within twelve hours after birth on Feb. 14, 1928. With a single sweep of the cataract knife a transection was made high up on the cord, and a red flush and vigorous stepping reflexes of the hind legs appeared at once. On February 21, there was complete anesthesia of the tail and hind legs with active reflex activity but no voluntary motion. On February 28, complete anesthesia persisted. Marked progression reflexes were elicited on pinching the tail, and the animal used its hind legs in walking. This probably had but little voluntary component, since the rhythm in the hind legs was often broken, and both hind legs frequently hopped together. On March 1, the sense of pain was present definitely in the left hind leg and doubtfully in the tail. Voluntary movements of the hind legs were probably present, since climbing over a finger was possible and coordination in walking was improved. Tactile sensation was absent. On March 2, the sense of pain was definitely present in both hind legs and the tail, and voluntary motion was improved. On March 10, the sense of pain in the left hind leg had reached normal acuity as compared with that of the fore limbs. Voluntary movements of the hind and fore limbs were well coordinated, as in climbing a cage or a finger. The right side was more agile than the left. Both ankles were weak and frequently turned laterally. On March 13, the sense of pain and voluntary motion in the right hind leg and tail had further improved. The animal climbed about freely, although at times it would drag its hind legs, which were still weak, for a few steps. On March 20, motor coordination was very good. Experienced observers had difficulty in picking this rat from its control litter mates (except by its full-sized tail). It spontaneously and repeatedly sat on its haunches and cleaned its face with its fore legs, while supporting itself entirely by the hind legs. The animal was killed and examined. Grossly, the cord appeared normal save for a slight adherence to the anterior wall of the bony canal. Microscopically, there was only a slight destruction of the superficial fibers of the anterolateral portion of the cord in the middorsal region, and connective tissue had penetrated into the slight indentation formed by the lesion. The dura in this region was markedly thickened. Whole red cells were abundant in the epidural and subarachnoid spaces at the site of the lesion, apparently freshly formed when the adhesions were torn on removing the cord. No abnormal fibers were seen. The remainder of the cord appeared absolutely normal at all levels. No evidences of regenerative end-bulbs or débris were found from any secondary degeneration above or below the lesion. Gross sections of the cervical cord stained for myelin sheaths revealed no change from the normal.

Rat P4.—This animal was operated on on March 17, 1928, the seventeenth day of a timed pregnancy. Five embryos were found. One was removed for histologic examination, which showed the intraspinal tracts to be developed. One rat had its tail cut for identification as a control and was not further disturbed; the other three were sectioned in the lower cervical region. On March 22, four baby rats were found. A was dead and somewhat macerated. Staining was difficult, but it was found that the cord was not completely cut, for there was a continuity of tissue in several sections which seemed in no way abnormal. B was the control and showed normal development. It was killed on April 3 when weighing 18 Gm. C had definite sensation of pain in the hind quarters; the animal squealed regularly when either hind leg or the tail was pinched. Imperfect voluntary motion of the hind legs was noted. The left leg was stronger than the right. Microscopic examination revealed a lesion that almost completely involved one half of the cord in its anterior portion. The lesion consisted of a sharply defined indentation with complete destruction of about 1 mm. of the cord, into which the leptomeninges had penetrated. The meninges were thickened and highly vascularized. No regenerative end-bulbs were

noted. The remainder of the cord was in no way abnormal. D showed complete paralysis and anesthesia of the hind quarters. This rat was kept alive from March 22 to April 3, during which time no change in function took place. It was found that there was a marked kyphosis in the upper thoracic region, so severe that abnormal mobility was present, and that the lower portion of the kyphosis was displaced dorsal to the upper. At first, edema was present in the lower limbs, but this gradually disappeared. The animal was emaciated and weighed only 7.5 Gm. when killed. Autopsy showed that the kyphosis was due to a complete severance of the vertebral column with the ends not approximated. The ends of the cord also were separated. The configuration of the cord was histologically normal. From the proximal stump could be seen a few coarse, irregular axons growing into the meningeal adhesions in a disorderly fashion.

RAT P_2.—This animal was operated on on March 17, 1928, the seventeenth day of a timed pregnancy. Seven embryos were found, one of which was removed for histologic study, one was kept as a control (with its tail cut), and the other five were transected. On March 22, six living rats were born. The control developed normally until April 4, when it was killed, at which time it weighed 21 Gm. Examination of A revealed complete anesthesia of the hind legs and trunk to the xyphoid process. The animal kept its tail curled between its legs and its hind legs sprawled. It was unable to right itself when turned on its back. Its reflexes were lively; when the tail was pinched quickly, stepping movements started in the hind legs which beat twice a second for from thirty to sixty seconds. These movements were identical with those already described, which had appeared at the time the cord was severed. Gross dissection of this animal showed a normal vertebral column, but the ends of the cord at the site of the lesion were not approximated. In B the sense of pain was definitely shown by the animal's squealing when the hind legs or the tail was pinched. The posture was normal. When placed on its back, the rat easily turned over with normal coordinated movements of the hind legs. It was killed at once. Grossly and microscopically, no evidence of any lesion in the meninges or cord was obtained. No regenerative or degenerative phenomena, as described by Cajal, were observed. In C a definite, normal sense of pain, normal posture and righting movements of the hind quarters were present. Seven days later, voluntary movements of the hind legs revealed that the left was more perfectly controlled than the right. Microscopically, an almost complete hemisection of the cord was found, with marked secondary degeneration below the lesion. The leptomeninges were markedly thickened. D was completely anesthetic below the lesion, with posture and motion like B. On March 24, it was still anesthetic below the lesion, although a suggestion of voluntary motion of the right hind leg appeared in righting itself, which was not noted later. A marked spinal deformity was present. The spine below the lesion was displaced laterally and dorsally. The animal was killed on April 4, when it weighed 11 Gm. The ends of the cord were not approximated, and microscopic examination revealed no evidence of regenerative attempts. In E a definite sense of pain, normal motion and posture were present at birth; development was normal to a weight of 19 Gm. on April 4, when it was killed. Microscopic examination showed only a slight lateral lesion of the cord with invading connective tissue into which axonal ends had penetrated. These were tortuous and thick and revealed regenerative end-bulbs.

Third Series of Experiments (1928).—Twenty female rats were allowed to become pregnant at definite times. The pregnant animals were operated on in the usual manner from two to five days before term. The embryos were killed in from one to five days after operation. One hundred and seventy-three such

embryos were obtained, only fifty of which were suitable for study. Serial sections were made of the whole embryo or of the spinal column to determine histologically whether attempts at regeneration were present.

The very young embryos had spinal cords consisting of a rather homogeneous spongioblastic matrix in which were embedded primitive neuroblasts. The cord was frequently completely cut in two, but no degenerative changes were found in either segment. Each seemed morphologically a unit and independent of the other. The reason for this was the obviously early embryonic stage of the nerve tissue, a stage before descending or ascending pathways had appeared. At the site of the lesion the usual mesodermal reaction to trauma was observed.

In some cases the older embryos reacted differently. A severe degeneration of tissue in either direction from the transection took place in these. This reaction was more than a simple degeneration of the fibers disconnected from their cell bodies; it was a reaction of the whole tissue. In other cases such a disintegration of the cord had not taken place, but at the margins of the cut ends progressive glial reactions were noted. These had resulted in the formation of strands of gliosis, none of which, however, had bridged the defect.

Of great interest was the observation that even in cases with separation of the cut ends of the cord, in which approximation of the knife wound had been good and the vertebral bodies were not dislocated, no evidence of scar could be found in the skin, subcutaneous tissues, muscles or vertebrae. The knife wound in these structures had healed completely, leaving no histologic traces.

COMMENTS ON RESULTS

The results recorded for rats 7, 25, P_2 (A, C and E) and P_4 C are not isolated observations, but are selected from many similar experiments in which rats supposedly transected in utero several days before birth showed varying degrees of sensation of pain and voluntary motion of the hind quarters at or shortly after birth. A much larger number of experiments yielded no results, for many litters were born dead, resorbed in utero or very often eaten by the mother. In the experiments on new-born rats, many died from various causes. Of the survivors, only two rats (L6 and 24) showed a marked return of function after an initial period of a week or more during which analgesia and absence of voluntary motion were complete; one of these (rat 24) was lost before autopsy. Fifteen rats with incomplete lesions showed striking improvement with the passage of time, but the physiologic evidence alone in such cases cannot be given great weight because of the probability of reeducation. Many rats operated on in the lumbar region during the first days of life showed no return of function during several weeks of observation. Some of these had vertebral deformities.

A priori, one would expect a transection of the cord to be accompanied by visible morphologic changes persisting for some time after the lesion was made. For example, a spinal transection is impossible without the severance of one or more of the longitudinally placed meningeal vessels, with considerable bleeding, which is known to cause severe meningeal reaction. Thus we have found a hyperplastic reaction

of the meninges at the point of injury, whether the demonstrable lesion in the cord was only a slight nick or a complete transection. It seems more likely, therefore, that an intact cord without meningeal reaction represents a case in which no lesion was produced rather than one of complete regeneration. Yet such observations were associated with severe functional disturbances.

The cords of many animals operated on in utero remained entirely separated, not being connected even by fibrous tissue; often this was due to vertebral displacement or interposing tissue. These cases are interesting in that no adequate evidence of even an attempt at regeneration of the cut axonal ends could be seen. Only a few irregularly interwoven fibers embedded in connective tissue were found.

Another situation was presented by rats operated on in utero and clinically appearing normal. The majority of these rats revealed only partial lesions consisting of defects in the anterolateral white substance or small superficially placed cavities. These lesions showed no evidence of active degeneration, an observation in harmony with the work of Spatz, who found the "Abbau" in the central nervous system of newborn kittens to be exceedingly rapid and complete, frequently leaving a cavity or a lateral nick as the only trace of the process. Evidence of active regeneration in the cut axonal ends was carefully sought, but no regenerative figures were found. This is not surprising, for the time element in these cases was too great. Only a few apparently newly formed fibers were found crossing a lesion or embedded in the meningeal adhesions. The results in our third series showed that any attempt at regeneration had quickly subsided even after a central injury, a continuous attempt being absent.

Similar abortive attempts at the formation of new fibers have been described by Cajal and others in experimental animals and even in the tissue of the central nervous system in human beings following disease or injury. Cajal [5] described accurately the attempts at growth in cut central axons, and stated that they appear more often in connection with a connective tissue scar:

> There exists a certain parallelism between the regenerative reaction of the white matter and the presence and proximity of the cicatricial mesodermal formations. Very small punctures and fine wounds which are partial, in the gray and white matter, and which are rapidly cicatricized by means of neuroglial tissue hardly ever bring about a sprouting of axones; even the traumatic degenerative process is precarious and of slight extent. On the contrary, complete interruptions of the cord, with an eruption of exudates and an abundant proliferation of the mesodermal cells of the dura and pia mater, followed by an application and even a partial penetration of the connective tissue scar into the lips of the white matter,

5. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, New York, Oxford University Press, 1928.

are apt to bring about, not only the appearance of nerve sprouts, but even their active migration from the region of the cord into the connective tissue scar, and in certain cases even into the nerve roots. It thus seems natural to conjecture that the regenerative process of white matter, which is so remarkably faint and sluggish under ordinary conditions, *can be powerfully stimulated by means of active or trophic substance liberated by the mesodermic scar and diffused in the spinal nerves and their edges.*

Growth of Rats on Which Operation Has Been Performed.—Animals operated on in utero or at birth that remain partially or completely without function below the lesion in the cord were regularly smaller than the rats not operated on or the rats that had recovered. This deficit in weight was from 20 to 30 per cent, although rat P_4D, the extreme case, was 60 per cent lighter than its normal litter mate. During the first weeks of life this difference in weight might well be explained by poor nutrition, since the normal rats nose out the deficient ones from the mother's nipples. The deficiency persisted, however, after the animals had been on an abundant stock diet for several weeks. Whether this was due to muscular atrophy or to a "trophic disturbance" cannot be stated.

Bladder Control.—In adult animals, spinal section was always followed within a week by a huge distention of the urinary bladder, with subsequent hydro-ureters and hydronephrosis. In sharp contrast, the bladder remained normal in the new-born animals with transected cords. The difference apparently lay in different conditions of reflex control. The older rats had paradoxical incontinence, whereas the young rats emptied their bladders frequently as part of a reflex response of the isolated spinal cord. A combination of vasomotor disturbance and urinary retention probably caused the severe edema and moist gangrene often seen in the hind legs of the adult rats. This was rarely seen in the young ones. For prolonged studies on the isolated spinal cord, young rats seem to offer favorable opportunities.

Spinal "Release."—It is well known that young animals do not exhibit nearly the same degree of spinal shock following transection as do adults of the same species. This is illustrated in a striking manner in the present experiments. From the instant of high transection newborn rats show no gross signs whatever of spinal shock; on the contrary, they exhibit an enhanced reflex activity of the isolated cord similar to the third stage observed in man when the mass reflex can be elicited. A strong stimulus evokes a general motor discharge, including contraction of the bladder and often of the rectum. These animals also show a much nicer reflex control, for a variety of local or general responses can be obtained. Reference has already been made to walking, jumping and defense thrust reflexes. The well known flexion of a

leg following a painful stimulus is very active. The contralateral leg usually executes rhythmic stepping movements as part of this reflex, rather than passing into maintained extension. M. W. Gerard and one of us (R. W. Gerard) [6] have also observed dorsal, ventral and lateral flexion of the entire tail or of only its tip, spreading of the toes of one foot, adduction and abduction of a foot or an entire leg, flexion and extension at single joints, etc., in response to local painful or tactile (stroking) stimulation.

The whole picture is definitely one of release of the lower reflex centers from cephalad control. It should follow from this that in the new-born rats such a high control is already present and that the long spinal paths are functional. This is of importance in evaluating other results. Furthermore, the absence of spinal shock cannot be entirely explained by assuming that the lower centers are still entirely autonomous and therefore not affected by the section of tracts above them.

The mechanism of the spinal release remains unknown and need not be considered in this paper. This point is briefly discussed by Gerard and Forbes,[7] and it may be recalled in this connection that the after-discharge of excitatory reflexes in these young spinal rats may last for a minute or longer.

Reorganization of Functional Pathways.—A number of rats subjected to partial spinal section showed a rapid and almost perfect return of function. This improvement might be attributed to anatomic repair or to functional recovery. The vicarious taking over of function by other centers in the case of lesions in the motor cortex needs no comment, and Lashley's [8] work on the rat has served to emphasize the physiologic plasticity of even the adult nervous system. That some type of pattern reorganization in the partially isolated cord may take place is shown in these experiments. In rat 6, for example, restitution of function was practically complete, although the cord showed extensive defects. This plasticity would naturally be greatest in young tissue, and we have not felt justified in attributing improvement in function in animals with incompletely transected cords to anatomic restitution. The voluntary motion of a muscle above the lesion may cause tension in the wall of the body which is an adequate reflex stimulus to some muscle below the lesion, thus causing coordinated movement.

---

6. Gerard, M. W., and Gerard, R. W.: Unpublished data.

7. Gerard, R. W., and Forbes, A.: Fatigue of the Flexion Reflex, Am. J. Physiol. **86**:186, 1928.

8. Lashley, K.: Brain Mechanisms and Intelligence, Chicago, University of Chicago Press, 1930.

It is difficult to see, however, how movements of the hind legs preceding other movements and giving every appearance of being voluntarily initiated can be accounted for in this manner. A case in point is seen when a rat that has been hanging quietly from a finger by its fore legs begins "searching" movements with its hind legs for support, which may be repeated with pauses time after time until support is found. Also the prompt and regular response of the whole animal, including squealing, to a painful pinch of the tail would seem to demand conduction in the spinal cord, especially as this was never observed in animals known to have complete spinal transection.

GENERAL COMMENT

The second half of the past century witnessed numerous studies on degeneration and regeneration of the spinal cord and brain following injury. A great variety of animals was used, and the most conflicting results were reported. In the last twenty-five years, the question has been practically dropped and the view universally adopted that regenerative processes in the central nervous system of higher vertebrates do not occur. However, even though many careful workers obtained absolutely negative results both functionally and histologically, other seemingly careful studies yielded definitely positive ones.

Failure of central regeneration is usually attributed to two factors acting together or independently: the rapid formation of a dense connective tissue scar in a wound, which mechanically obstructs fiber growth, and the absence of neurilemma sheaths, which are assumed to be essential to fiber regeneration. So far as we are aware, the evidence for the latter assumption is the failure of central regeneration (a rather backhand argument) and histologic studies on the neurotrophic and supporting function of the neurilemma in regenerating peripheral nerves.

A number of lines of investigation tend to throw doubt on these interpretations. Ranson,[10] who reviewed the older work, demonstrated in young rats that nerve fibers can cross the site of a lesion in the brain. He made a stab wound through the dorsal part of the cerebral hemisphere down to the corpus callosum, and after six weeks obtained sections of the injured region. He found "(1) the absence of adhesions in the meninges, (2) absence of a well defined connective tissue scar, (3) the atrophy of sectioned nerve fibers on the cell body side of the injury, (4) the distortion of the wound due to the shifting of areas in the growing cortex and (5) the presence of nerve fibers crossing the site of the lesion." The younger the animal, the more favorable were the

9. Reference deleted by authors.

10. Ranson, S. W.: On the Medullated Nerve Fibers Crossing the Site of Lesions in the Brain of the White Rat, J. Comp. Neurol. **13**:185, 1905.

results, and in one rat operated on on the day of birth the path of the knife through the upper part of the cortex had been obliterated, a scar in the deeper region giving the only indication that a knife had passed through the upper part. The brain of a rat that was operated on when 3 weeks of age showed a much more prominent lesion. Ranson expressed the belief that the new fibers were formed by the growth of cells undeveloped at the time the lesion was made rather than by regeneration of injured fibers.

Dunn [11] extended these operations on 10 day old rats by transplanting slices of cortex which survived, and he found nerve fibers crossing the line of transplant.

Eichorst [12] sectioned the spinal cords of three puppies a week after birth (by laminectomy and lifting the cord to insure complete section), and in one obtained coordinated use of the hind legs in walking and standing that, he was convinced, was voluntary. Sensation did not return. Grossly, the continuity of the cord was reestablished, and the microscope demonstrated numerous fibers crossing the site of the lesion. He also described reflex activity at the time of section very similar to that which we have observed in baby rats.

That immature developing nerve cells do not require neurilemma for the outgrowth of their fibers is proved by the tissue culture experiments of Harrison [13] on frog embryos and of Burrows [14] on chick embryos. Also, severe operative manipulation in these early stages does not prevent the development of nerve cells or cause an overgrowth of connective tissue cells which might smother them. In the rat, the nervous system at birth is still far from maturity. Abundant mitoses of neuroblasts are present in a 4 day old rat (Hamilton [15]). Allen [16] found mitoses in the cord for twelve days, and that growth of fibers in the dorsal roots continues into maturity (Hatai [17]). Five days before birth, the nervous system is very immature.

11. Dunn, E. H.: Primary and Secondary Fndings in a Series of Attempts to Transplant Cerebral Cortex in the Albino Rat, J. Comp. Neurol. **27**:565, 1916.

12. Eichorst, H.: Ueber Regeneration und Degeneration des Rückenmarkes, Ztschr. f. klin. Med. **1**:284, 1879.

13. Harrison, R. G.: The Outgrowth of the Nerve Fiber as a Mode of Protoplasmic Movement, J. Exper. Zool. **9**:787, 1910.

14. Burrows, M. T.: The Growth of Tissues of the Chick Embryo Outside the Animal Body, with Special Reference to the Nervous System, J. Exper. Zool. **10**:61, 1911.

15. Hamilton, A.: The Division of Differentiated Cells in the Central Nervous System of the White Rat, J. Comp. Neurol. **11**:297, 1901.

16. Allen, E.: The Cessation of Mitosis in the Central Nervous System of the Albino Rat, J. Comp. Neurol. **22**:547, 1912.

17. Hatai, S.: On the Origin of Neuroglia Tissue from the Mesoblast, J. Comp. Neurol. **12**:291, 1902.

In the lower forms, full regeneration of the spinal cord following transection has been well established by Detweiler,[18] Hooker [19] and others. Hooker found regeneration even in adult frogs. Pearcy and Koppanyi [20] presented evidence of restoration of function in fish, following spinal section, but this work has not been confirmed by Hooker.[21] Regeneration of central nervous tissue in the adult rat has been reported by Koppanyi, who enucleated and replaced the entire eyeball. In three such rats, in which both eyes had been operated on, Koppanyi and Baker [22] obtained a return of pupillary reflexes and evidence of vision. Kolmer [23] reported numerous nerve fibers in the reformed optic nerve of one of their rats.

There thus appears to be good evidence of spinal regeneration in amphibia and other lower vertebrates, and reported regeneration of the optic nerve in adult rats, as well as the older claims of spinal regeneration in birds and mammals. There appears no *a priori* reason for considering repair in the spinal cord in new-born or embryonic rats as impossible.

It may be stated at once that, considered independently, the physiologic results are largely positive, the histologic negative, and the interrelations between them peculiarly confusing. That nerve fibers can grow across a complete spinal lesion seems certain from rat 11, in which numbers of fibers were found in the strand of tissue bridging a large defect in the cord. That separation was at first complete is shown by the bony deformation which must have followed a complete lesion of the spinal column with displacement. No functional studies of this animal were possible as it was found dead.

In rat 6, the remarkable central integrity of the nerve fibers with a circumscribing lesion would seem to depend on incomplete section, though the central integrity is difficult to understand and slight function remained in the hind quarters from the start. Subsequently, an almost

18. Detweiler, S. R.: Experimental Studies on Morphogenesis in the Nervous System, Quart. Rev. Biol. **1**:61, 1926.

19. Hooker, D.: Studies on Regeneration in the Spinal Cord: II. The Effect of Reversal of a Portion of the Spinal Cord at the Stage of the Closed Neural Folds on the Healing of the Cord Wounds, on the Polarity of the Elements of the Cord and on the Behavior of Frog Embryos, J. Comp. Neurol. **27**:421, 1917; IV. Rotation About Its Longitudinal Axis of a Portion of the Cord in Amblystoma Punctatum Embryos, J. Exper. Zool. **55**:23, 1930.

20. Pearcy, J. F., and Koppanyi, T.: A Further Note on Regeneration of the Cut Spinal Cord in Fish, Proc. Soc. Exper. Biol. & Med. **22**:17, 1924.

21. Hooker, D.: Physiological Reactions of Goldfish with Severed Spinal Cord, Proc. Soc. Exper. Biol. & Med. **28**:89, 1930.

22. Koppanyi, T., and Baker, C.: Further Studies on Eye Transplantation in the Spotted Rat, Am. J. Physiol. **71**:344, 1925.

23. Kolmer, W.: Die Replantation von Augen: V. Histologische Untersuchungen an transplantierten Augen, Arch. f. mikr. Anat. **99**:64, 1923.

complete recovery of function was achieved despite the still extensive anatomic lesion. Here some functional recovery by reorganization must have occurred.

Rat L6s afforded perhaps the most difficult problem. Operation was performed on this animal on the day of birth and at the time satisfied all the criteria for a complete section. The completeness of the lesion was further testified by the examinations during the succeeding two weeks, which showed the hind quarters of the rat to be entirely anesthetic and not under control from the higher centers. Then function gradually and progressively returned until the rat behaved in a practically normal manner at the end of five weeks, showing a definite sense of pain in the hind legs and tail, and using its hind legs in apparently perfectly coordinated, voluntary acts involving the whole body or the hind limbs alone. Grossly, except for delicate ventral adhesions and possibly a slight enlargement at the level of operation, the cord was apparently normal, and microscopically, only an insignificant lateral defect was noted; otherwise, the cord appeared to be normal. There can be no question of the initial absence and later return of function in this rat. We are confronted, therefore, with several improbable alternative interpretations. Either the cord was not cut and the temporary disturbance of function was secondary to general operative trauma, a blood clot compressing the cord and gradually becoming organized and absorbed; or the cord was cut and repair was so perfect as to leave hardly a trace. The immediate symptoms accompanying section and the entire loss of function as well as the exposed position of the organ indicate that there was not a complete failure to section the cord. General experience in neuropathologic conditions and our own findings on other animals make it appear improbable that anatomic healing occurred.

In the case of fetuses operated on in utero, in animals with complete section which lived for some weeks, or in those which lived only a few days, the usual anatomic concomitants of regeneration were not found on the ends of the cut axons, though marked physiologic improvement often was observed.

In view of the evidence of our experiments, we conclude that far-reaching physiologic reorganization occurs in the young mammalian nervous system after severe lesions, which may lead to restitution of a great deal of function. We cannot conclude from our work that a significant central regeneration is possible, although the question is open for final proof.[24]

24. Since this paper was sent to press, the complete report by D. Hooker and J. S. Nicholas has appeared (Spinal Cord Section in Rat Fœtuses, J. Comp. Neurol. **50**:413, 1930), and they give entirely negative results. An exactly opposite conclusion that regeneration occurs, is reached by Milliavacca (Arch. Inst. Biochem. Ital. **2**:201, 1930).

SUMMARY

In a series of experiments on new-born rats and on fetuses in utero, the spinal cords were transected by a single clean cut with a cataract knife, and subsequently studied histologically, the "clinical" course of the animals being carefully observed during the interim. Many experiments yielded negative or no results because the animals died or the spinal column became displaced, etc. Several rats operated on at birth, however, gave evidence of a gradual return of function. One animal, studied with special care, which showed evidence of a complete section at the time of operation, was entirely paralyzed and anesthetic below the lesion for two weeks, while in a subsequent three weeks the recovery of sensation and voluntary motion was practically complete. The spinal cord of this animal showed no evidence of a lesion. Several rats operated on in utero were born from five days to a week later with the sense of pain, voluntary motion or both present in the hind quarters. The spinal cords showed partial lesions or none at all. We cannot decide on the correct interpretation of these cases.

The possibility of the growth of nerve fibers into and across a lesion after a complete or partial transection is definitely established.

The immature spinal cord also possesses remarkable powers of physiologic reorganization which may lead to full return of function below an almost complete separation of the cord.

A consideration of the evidence bearing on regeneration in the mammalian central nervous system from other sources as well as from our own results indicates that although some growth of nerve fibers from the cut end of axons may appear, return of function due to anatomic regeneration has not been proved.

INJURY AND REPAIR WITHIN THE SYMPATHETIC NERVOUS SYSTEM

I. THE PREGANGLIONIC NEURONS *

SARAH S. TOWER, M.D.
AND
C. P. RICHTER, M.D.
BALTIMORE

The preganglionic sympathetic nerves, like other peripheral nerves, are endowed with a capacity for regeneration. The work of Langley,[1] Tsukaguchi,[2] Lee [3] and others has shown that a lesion—even a large defect—in such nerves is quickly repaired by new growth of axis cylinders. Furthermore, the speed of regeneration compares favorably with that of somatic motor nerve fibers. In most of this work the cervical sympathetic cord and the ocular functions that it serves were utilized. For the sympathetic innervation of other regions, functional tests yielding satisfactory quantitative data were not available. However, the recent development of methods for measuring the electrical resistance of the skin and especially for following the negative variations in the electrical potential of the skin, of central origin, the spontaneous waves and the "galvanic skin response," now allows accurate study of sympathetic function in relatively hairless surfaces of the skin.

Skin-resistance, as the term is used in this paper, is the resistance offered by the body to the passage of a small galvanic current. The high values found for skin-resistance, in contrast with the low values for true resistance of the body, depend on the employment of a constant current, with the attendant polarization and generation of counter currents in the tissues. This reenforced resistance is concentrated in the skin (Richter,[4] 1926), for if the skin under the electrodes is punctured by the finest needle or the intactness of the epithelium is assailed in any way, the resistance is at once nearly eliminated.

---

* Submitted for publication, Dec. 3, 1930.

* From the Anatomical Laboratory of the Johns Hopkins University and the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital.

1. Langley, J. N.: J. Physiol. **12**:347 and 375, 1891; **22**:215, 1897; Cinquanten. de la Soc. de biol., 1899, p. 220; J. Physiol. **25**:364 and 417, 1900.

2. Tsukaguchi, R.: Quart. J. Exper. Physiol. **9**:280, 1916

3. Lee, F. C.: Physiol. Rev. **9**:575, 1929.

4. Richter, C. P.: Proc. Nat. Acad. Sc. **22**:214, 1926; Brain **50**:216, 1927; The Electrical Skin Resistance: Diurnal and Daily Variations in Psychopathic and in Normal Persons, Arch. Neurol. & Psychiat. **19**:488 (March) 1928.

The spontaneous waves and the galvanic skin reflex are action currents generated in the skin. It is not known how the more or less rhythmic spontaneous waves originate. Their frequency is usually too low to allow correlation with respiration or heart beat. The galvanic skin reflex is the sudden drop in the potential of the skin accompanying emotional activity in the human being or following a nocuous stimulation, such as pin prick or pinching of the tail, in the experimental animal. Both of these action currents probably represent activity on the part of the sweat glands.

By experiments on cats and monkeys, Richter[5] (1929) demonstrated the dependence of these functions on intact sympathetic innervation and their independence of somatic innervation. Therefore, in spite of the occasional absence of spontaneous waves and rarely of the galvanic reflex in normal persons, it seemed that these activities, together with the measurements of the resistance of the skin might afford a sensitive and sure index to sympathetic innervation. Experiments were planned to investigate the applicability of this method to the study of injury and repair within the sympathetic nervous system. The results on the preganglionic neuron are presented in this paper.

MATERIAL AND METHODS

Twenty-seven adult cats were used for the experiments. Because of its accessibility, the right stellate ganglion was selected as the point of operative attack on the sympathetic neurons supplying a paw pad. All surgical procedures were carried out under ether anesthesia. The ganglion was reached through an incision parallel to the caudal border of the scapula, allowing access to the vertebral end of the first intercostal space. After the ribs had been retracted, the ganglion was usually immediately in view, being spread out so that each of its branches could be identified and cut at will: the white and gray rami of the first and second thoracic nerves, the vertebral nerve, the two portions of the ansa subclavii, the one or two strands passing to the heart and lungs and the thoracic sympathetic trunk. In order to section the sympathetic trunk low down, between the third and fourth thoracic or between the fourth and fifth thoracic nerves, entry was made at the vertebral end of the corresponding intercostal space.

A potentiometer and string galvanometer were used to determine the resistance to the passage through the body of a constant current of 1 milliampere. The presence or absence of spontaneous waves and a galvanic skin reflex were recorded on bromide paper by means of the galvanometer string. The technic of applying the electrodes and of taking the records was in every respect similar to that described by Richter (1929).[5] The different electrode led off from the central paw pad; the indifferent, from the pinna over the site of a puncture in the skin. Records were always taken in sequence from the pads of the right and left fore paws. In some of the animals the pads of the hind feet were examined as well. At the same time, the rectal temperature was determined. Records were taken

5. Richter, C. P.: Am. J. Physiol. **88**:594, 1929; Bull. Johns Hopkins Hosp. **45**:56, 1929.

twice a week, as a routine procedure, and more frequently in the week after operation, and as regeneration was approaching completion. As the readings were taken they were entered on large graphs on which rectal temperature was also plotted.

A note on the use of the galvanometer string must be made. The two strings used to obtain most of these records had resistances of 6,500 and 5,400 ohms. Before each reading of skin-resistance was made, the tension of the string was standardized so that an electromotive force of 1 millivolt produced a deflection of 1 cm. on the scale. The animal was then introduced into the circuit; any resting current was compensated, and by increasing the electromotive force the same end-point was attained. By applying the formula [5] $R = S\ (N - 1)$, in which R is the resistance of the animal, S, the resistance of the string and N, the number of millivolts necessary to deflect the string 1 cm., the resistance introduced into the circuit by the animal was calculated.

The galvanic skin response will register at the string tension used for the records of skin-resistance and the spontaneous waves also, if they are active and in phase. But for the routine examination of these functions the string was loosened until 10 millivolts gave a deflection of 2.5 cm. This was sensitive enough for all normal conditions and when the resistance of the paw operated on was less than 162,000 ohms. By further loosening the string, however, the presence or absence of the galvanic reflex and spontaneous waves could be determined for even higher levels of skin-resistance, up to 413,000 ohms.

Control.—The determinations of skin-resistance, spontaneous waves and galvanic skin reflex that were invariably made on the pad of the left normal fore paw at the same time as on the pad of the right fore paw, which was affected by the operation, afforded rigid control on conditions in the latter. Normal resistance of the palmar skin in the cat ranges between 2,500 and 30,000 ohms. In this series of records the resistance of the pad of a normal fore paw exceeded 30,000 ohms only once without obvious explanation. After operation and during illness, such as pneumonia, pleurisy or sepsis, the resistance may be high. But even in these conditions, resistance in a normally innervated paw pad rarely exceeded 200,000 ohms.

The action currents of the skin were less constant. Any departure of the animal's condition from normal, high or low temperature, for example, tended to suppress the spontaneous waves, and they were frequently absent on the day after operation. The galvanic skin reflex was more dependable. Eighteen of twenty-seven cats did not at any time fail to show the reflex when they were tested on the normal paw, and in only four was the reflex inexplicably absent (in three, for one isolated determination only; in the fourth, four times at intervals during the six weeks of observation).

The chart of rectal temperature afforded a control of another sort.

OBSERVATIONS AND INTERPRETATION

Section of All Preganglionic Sympathetic Fibers Passing to or Through the Stellate Ganglion in Sixteen Cats.—Although in two animals the attempt was made to discriminate between the white and the gray rami of the first thoracic nerve and to cut the white only, in the remaining fourteen the gray rami of the first and second thoracic nerves were cut, together with the white rami and with the thoracic sympathetic trunk. To ensure that the gray rami passing to the cervical nerves as the vertebral nerve were by themselves capable of main-

taining the resistance of the skin in the central paw pad at a normally low level and of transmitting the spontaneous waves and galvanic skin reflex, the white and gray rami of the first and second thoracic nerves were cut in two cats, leaving the vertebral nerve alone intact. The skin-resistance was not increased and there was no interference with spontaneous waves and galvanic response.

The effect of sectioning all preganglionic fibers passing to the stellate ganglion was threefold. Spontaneous waves were eliminated from the records of resistance of the skin. The galvanic skin reflex could no longer be elicited. The skin-resistance was increased to many times the normal maximum.

The effect on the action currents of the skin was immediate and total. These activities were gone and did not reappear until regeneration could be accomplished. In a single case in which the galvanic reflex was recorded within the first week, the obvious explanation, incomplete operation, was confirmed by observations at autopsy. The galvanic skin reflex and spontaneous waves proved, however, less satisfactory for study than had been hoped, because much of the time the skin-resistance was too high to allow of their registration. During the first two days after operation, these functions could be examined in only six of the sixteen animals. Later, however, as the resistance dropped, the reflex could usually be repeatedly tested for long before the action currents of the skin reappeared.

On the other hand, the effect on the skin-resistance was only in part immediate, requiring time for its complete development. Thus, for example, in two cats, readings of resistance about an hour after operation, which was as soon as the animals recovered from the effects of the ether, were 253,000 and 63,000 ohms; the next day they were 383,000 and 900,000 ohms, and on the second day after the operation, they were each 2,100,000 ohms. And in general, though the skin-resistance was at once raised by operation to from 2 to 10 times the normal maximum, in the course of several days figures even 100 times this normal maximum figure were obtained.

Eight cats were followed from the time of section of the preganglionic fibers entering the stellate ganglion until the resistance again approached normal and the action currents of the skin reappeared, and for several weeks thereafter. Chart 1 presents records of three of the eight, illustrating the extremes of high and low resistance and the mean. The three records were selected for absence of complicating factors; the cats were healthy throughout; the resistance of the pads of the normal fore paws never exceeded 18,900 ohms; regeneration was prompt. The records show better than description the modification of resistance with the passage of time after operation. It is immediately obvious that the mounting resistance of the first few days soon reached a peak. In the

series of eight this peak occurred variously on the second to fifth days. The resistance then fell off, with perhaps one or more sharp rises later, and a gradual downward course characterized the second and third weeks (in two cases the downward course was prolonged to the fifth and sixth weeks). Finally, a last drop of several hundred thousand ohms brought the resistance to a level less than 200,000 ohms, and at once or in a few days, action currents reappeared.

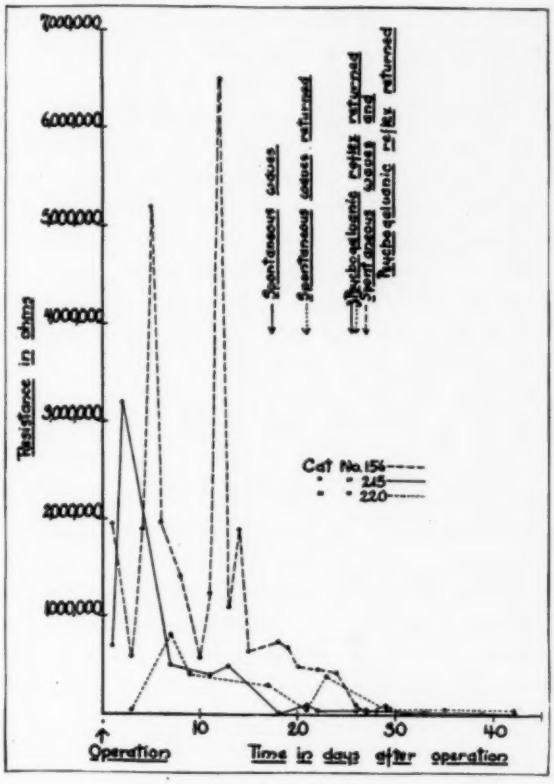


Chart 1.—Records of skin-resistance of the pad of the fore paw for six weeks after the section of all preganglionic nerve fibers passing to the stellate ganglion. The arrows at the top of the graph indicate the date of reappearance of spontaneous waves and galvanic skin reflex in the record similarly charted. In no case and at no time did the resistance on the pads of the normal fore paw exceed 18,900 ohms.

The Level of Entry Into the Thoracic Sympathetic Trunk of the Preganglionic Fibers Controlling the Skin-Resistance and the Galvanic Skin Reflex on the Pad of the Fore Paw.—The thoracic sympathetic trunk was cut between the levels of the first and second thoracic

nerves, and the second and third, the third and fourth and the fourth and fifth, two cats being used for each level. Chart 2 presents a record of each lesion. Section between the fourth and fifth thoracic nerves had only a slight temporary effect on the resistance and the

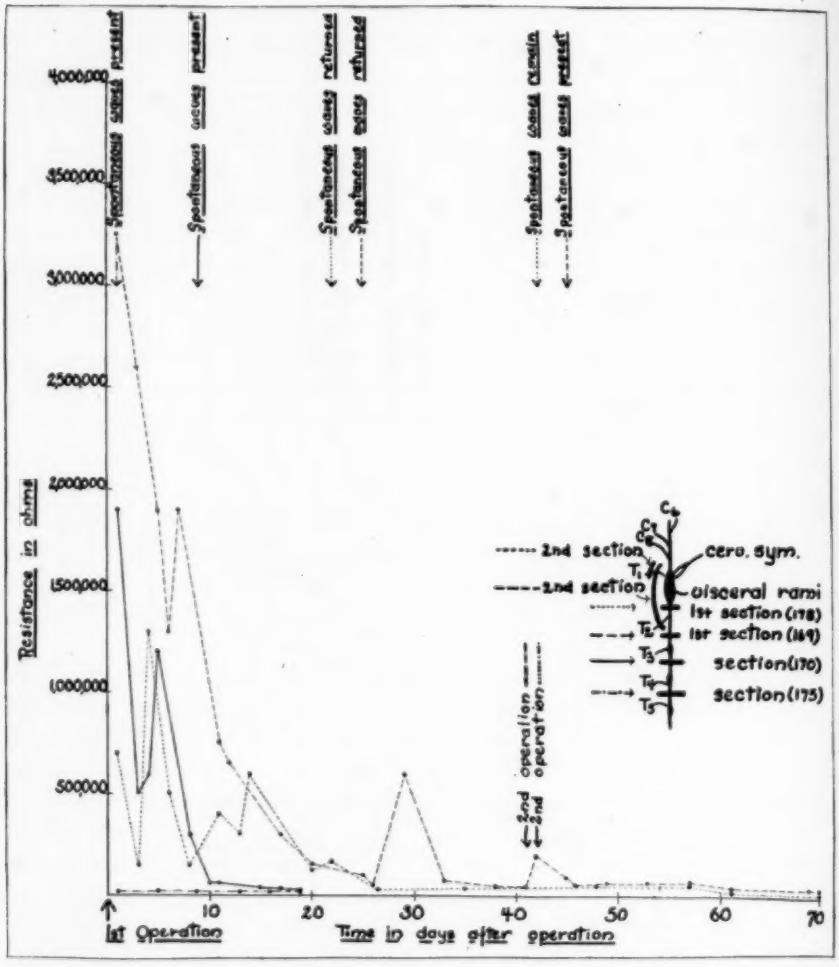


Chart 2.—Records of skin-resistance of the pad of the fore paw after section of the thoracic sympathetic trunk between the levels of the fourth and fifth thoracic nerves (cat 175), the third and fourth (cat 170), the second and third (cat 169) and the first and second (cat 178). The sketch indicates the point at which section of the trunk was done and of a second operation, when performed.

action currents of the skin. Cutting between the third and fourth thoracic nerves resulted, however, in a more enduring rise of resistance

and in suppression of the spontaneous waves and galvanic reflex for nine days (with levels of skin-resistance which would allow of testing). Section between the second and third thoracic nerves abolished the reflex and spontaneous waves for a longer period, twenty-one and twenty-five days, and the resistance was again increased. But characteristically, the resistance in each of these six records was highest on the first day after operation and decreased thereafter. It was only with section between the first and second thoracic nerves that the type of record of complete preganglionic section was suggested, resistance rising within the first twenty-four hours, but mounting higher thereafter.

Analysis of these records suggests the following conclusions: (1) The white rami of the first and second thoracic nerves are not able to transmit the galvanic skin reflex and spontaneous waves to the pad of the fore paw. It seems that the white ramus of the third thoracic nerve is not normally concerned with these functions, but is able to assume them after nine days (regeneration in this period seems out of the question; the length of trunk involved was several centimeters). Finally, the ramus of the fourth thoracic nerve, together with that of the first, second and third thoracic nerves, is able to supply these activities to the fore paw. This fact agrees with Langley's (1891) observation that the fourth thoracic nerve contains the first preganglionic fibers for the fore paw.

A difference between the production of action currents in the skin and the determination of skin-resistance begins to be apparent in these records of section of the trunk. For the maintenance of resistance of the skin at a normally low level, as for the galvanic skin reflex and the spontaneous waves, no central connections below the fourth thoracic nerve are required. (It should be remembered, however, that the resistance is being read from the entire surface of the central paw pad and that probably the presence of any normally innervated area on the pad, however small, will confer the quality of normality on the record.) But in contrast with spontaneous waves and reflex, although any lesion above this level affects the skin-resistance, any connection with the central nervous system through white rami seems able to moderate it. Thus, section of the trunk between the first and second thoracic nerves did not produce the resistance curve typical of complete preganglionic section, although the galvanic skin reflex and spontaneous waves were abolished. It is difficult to guess what influence is at work. According to Langley's studies, the fibers contained in the white ramus of the first thoracic nerve pass to the superior cervical ganglion. Furthermore, Langley[6] showed in

6. Langley (footnote 1, third reference).

1899 that no commissural fibers pass back from the superior cervical ganglion to the stellate. Are collaterals involved, perhaps of fibers having to do with skin-resistance over the head and neck? Or is something transmitted to the periphery by way of the white ramus of the first thoracic nerve and the visceral branches to the lungs, the heart and the larger blood vessels? The answer cannot be supplied from the data in hand.

Regeneration of the Preganglionic Axon and Reconstitution of the Preganglionic, Postganglionic Synapse.—Eleven cats accomplished regeneration of the preganglionic-postganglionic connection. As pathognomonic of the effective reestablishment of the connection between the

Data on the Time of Reappearance of Spontaneous Waves and the Galvanic Skin Reflex, and the Resistance of the Skin at This Time

Number of Animal	Operation	Spontaneous Waves Reappeared		Psychogalvanic Reflex Reappeared	
		Days After Operation	Resistance in Ohms	Days After Operation	Resistance in Ohms
156	Complete section of all preganglionic fibers	27	26,000	27	26,000
164	Same	28	45,500	28	45,500
165	Same	50	102,600	50	102,600
195	Same	25	48,600	25	48,600
201	Same	41	156,600	48	183,600
215	Same	26	102,600	26	102,600
220	Same	18	156,600	26	48,600
221	Same	26	156,600	26	156,600
178*	Section of trunk between first and and second thoracic nerves	20	102,600	22	156,600
129†	Section of trunk between second and third thoracic nerves	21	156,600	21	156,600
169†	Same	25	123,500	25	123,500
	Average	28	107,018	29	104,564

* Cat 178: At a second operation on the forty-second postoperative day, the gray and white rami of the first thoracic nerve were cut. Resistance, spontaneous waves and galvanic skin reflex were not affected.

† Cats 129 and 169: At a second operation on the forty-first postoperative day, the gray and white rami of the first and second thoracic nerves were cut. There was a slight effect on the resistance of the skin and the galvanic skin response and spontaneous waves were suppressed for one or two days.

central nervous system and the periphery, the unquestionable presence either of the spontaneous waves or of the galvanic skin reflex was accepted. Very often spontaneous waves were suggested in the records a few days before their definite reappearance, but a certain fraction of the total central-peripheral connection must, in all probability, be working appreciably to influence the string. Skin-resistance was a less reliable index of regeneration. A continued low level, below 100,000 ohms, was as certainly pathognomonic of regeneration as the reappearance of the action currents. But brief, temporary intervals of low resistance, even below 50,000 ohms, were occasionally encountered.

The accompanying table presents the data on the time of reappearance of the spontaneous waves and the galvanic skin reflex in each of the animals completing regeneration, together with the resistance of the

skin at this time. The spontaneous waves returned, at an average, on the twenty-eighth day, the reflex one day later. The quickest recovery was eighteen days; the slowest, fifty. There is little or nothing in the records or autopsies to account for this difference in the time of regeneration. The slowest animal (cat 165), for instance, was ill with some obscure condition during the first ten days after operation. Perhaps this was the cause. But cat 164, with an average time of regeneration, twenty-eight days exactly, was very sick with snuffles and pneumonia during the entire course of the experiment and died seven days after the return of the action currents of the skin. In the record of the autopsy on this same cat 165, a "gap of about 4 mm. between the cut ends of trunk and ganglion" was noted. Perhaps the delay was required to fill this in. But in the record of cat 178 there was an exactly similar note, yet regeneration in this animal was unusually rapid. Furthermore, the animal that made the quickest recovery (cat 220) was shown at autopsy to have filled in a small interval, 2 mm., while each of the animals in which a perfect gross anatomic result was obtained (cats 195 and 169) required slightly longer for complete regeneration.

There is some evidence bearing on the rate of regeneration of the nerve fiber proper. In seven of these animals the trunk was cut at the lower pole of the ganglion; in four, the cut was made 5 or 6 mm. below this point. The average time of regeneration of the first group was twenty-seven days; of the second, thirty-one. The figures allow, therefore, four days for regeneration of 5 mm. The data are certainly too few for a reliable calculation of the rate of regeneration. But the implication is clear that the time of regeneration is consumed otherwise than in the reproduction of the length of the axons.

On section at the lower pole of a ganglion of average size, the length to be regenerated could not be more than 5 mm., even if the fibers had to return to cells situated in the extreme anterior end of the ganglion. (Only one of the animals showed a gap filled in at autopsy.) Taking Lee's (1929) figure of slightly less than a millimeter a day as the most conservative, in that the total time required for functional regeneration was divided by the distance covered, the regeneration of length within the ganglion could require at most a week. What then goes on in the remaining three weeks? In 1916, Tsukaguchi noted an interval of two or three weeks between the time of reappearance of fibers in the superior cervical ganglion and evidence of return of function in the eye. When Langley (1897) cut both cervical sympathetic nerves in a cat, but cutting the one 2.5 cm. lower than the other, he reached the conclusion that the "Place of section of the cervical sympathetic made a slight, but only a slight difference in the rate of regeneration of the nerve." The obvious conclusion is that regeneration of the sympathetic nerve

fibers proceeds rapidly; 1 mm. a day is probably a conservative estimate. Reconstitution of the synapse proceeds, on the other hand, very slowly, requiring several weeks for its completion.

The question at once arises: When is the synapse reconstituted? Is there a sudden making of contact, which at once puts the central nervous system in connection with the periphery? The spontaneous waves and galvanic skin reflex seem to behave in this manner. They are absent; then they are present. Or is regeneration, on the contrary, a gradually increasing capacity for transmitting influence from preganglionic neuron to postganglionic fiber? The data on resistance are indicative of the latter. This would explain why, very shortly after reaching a peak, the skin-resistance begins to decline and continues to decrease until the reappearance of the spontaneous and reflex waves clinches the evidence of regeneration. If regeneration were a suddenly achieved fact, one might expect the resistance to be maintained at the high level for several weeks, and then to drop rapidly to nearly normal. Readjustment in the periphery is an obvious suggestion. But after section of the postganglionic nerves (this work will be presented in the second part of this study) the resistance likewise reached a high level within the first few days, and this level was maintained, with fluctuations, for months.

There is, then, some influence being exerted by the intact postganglionic neuron on the periphery during the time of regeneration. Of course, it is possible that this involves the postganglionic mechanism and periphery alone, perhaps with humoral influences at work. But the progressive downward course and the reappearance of the spontaneous waves and then of the galvanic skin reflex most certainly suggest that each of these stages is an integral part of preganglionic regeneration. We should have to concede, then, to the synapse the capacity of progressively recovering function of some sort during a period of regeneration.

The Condition of the Skin of the Pads of the Paws and Sweating.—The effect of sectioning all of the preganglionic fibers passing to the stellate ganglion or the trunk above the level of the fourth thoracic nerve was immediately to abolish sweating on the paw concerned. After a time, there was often also the slightest flaky desquamation and a slight hardening of the pressure-bearing surfaces. But no gross atrophic changes were seen.

As regeneration seemed imminent, the pads were watched more carefully. The resistance approached normal levels; the galvanic skin reflex and the spontaneous waves reappeared, but sweating did not return. From two to six weeks after reestablishment of the skin reflex it was observed that the dryness of the paws slowly diminished. Even then, only one animal (cat 201, which survived operation twelve weeks)

recovered sudomotor function completely. The observations were of gross sweating: moisture perceptible to touch or sight. It is probable that sudomotor function returned before tactile or visual evidence of it. But the conclusion is obvious that for the study of sympathetic regeneration, the resistance and the action currents of the skin afford an immensely more sensitive index than gross observation of the activity of the sweat glands.

SUMMARY

The preganglionic sympathetic nerve fibers were cut on the right side before entry into the stellate ganglion in a series of twenty-six adult cats. Until the completion of regeneration and for from two to six weeks thereafter, records were taken of the skin-resistance of the fore paws and of the galvanic skin response. Observations on sweating were also made.

The effects of operation were: (1) the immediate elimination of the spontaneous waves in skin potential and of the galvanic skin response; (2) an immediate increase in skin-resistance. The resistance of the skin reached a peak many times the maximum normal figure between the second and fifth days after operation, and thereafter fell slowly and with fluctuation.

Between the third and seventh weeks, as skin-resistance again approached a normal figure, the action currents of the skin reappeared. This reappearance was taken as the time of reconstitution of the connection between the central nervous system and the periphery. It averaged twenty-eight days. Evidence of some form of function of the synapse is noted several weeks before this date.

The observations on sweating made at the same time indicate that the galvanic skin response is a far more delicate test for the presence of sympathetic innervation than gross observation of the activity of the sweat glands.

THE CHOROID PLEXUS AS A DIALYZING MEMBRANE

I. OBSERVATIONS IN EXPERIMENTAL HYDROCEPHALUS *

THOMAS I. HOEN, M.D.
BOSTON

The choroid plexus as a source of cerebrospinal fluid was suggested by Faivre [1] in 1854, yet, while the existence of this function was generally suspected, it was many years before convincing evidence became available. In the last few decades, however, contributions from the fields of chemistry, anatomy, embryology and physiology, as well as observations at the operating table, have added much to the knowledge of this fluid system. While no single observation has been of a conclusive nature, the summation of available evidence led to the general acceptance of the theory that the cerebrospinal fluid is a product of the choroid plexus and that it has a definite circulation, the movement being in the direction of the subarachnoid space from whence it is resorbed into the blood stream, the mechanism of resorption remaining in doubt. The earlier investigators considered the fluid to be a true secretory product, but more recent observations have cast doubt on the secretory hypothesis and indicate that eventually the physiology of the fluid may be found to rest entirely on physicochemical principles. The whole subject was carefully reviewed in a recent paper by Fremont-Smith [2] in which he considered all the available evidence as supporting the theory that the spinal fluid is a true dialysate, obeying the physical laws of osmosis, rather than a true secretion, and that it is comparable to the fluid in ascites and the pleural and synovial effusions.

If the fluid is a dialysate, its production should depend on four mechanical factors, the hydrostatic capillary pressure, the hydrostatic ventricular pressure, the osmotic pressure of the capillary blood and the osmotic pressure of the ventricular fluid. As a sequel to this, it is evident that any increase in ventricular pressure must be accompanied by a corresponding change in one or more of the other three factors. If the escape of fluid from the ventricles along the normal channels is prevented in any way (in these experiments the aqueduct of Sylvius was blocked), the ventricular pressure becomes increased as fluid continues

* Submitted for publication, Feb. 12, 1931.

* From the Laboratory of Surgical Research, Harvard Medical School.

1. Faivre, E.: Compt. rend. Acad. d. sc. **34**:424, 1854.

2. Fremont-Smith, F.: The Nature of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317 (March) 1927.

to be elaborated by the choroid plexus, the filtration pressure being maintained by the mechanism described by Fremont-Smith in which compression of the choroidal veins raises the choroidal capillary pressure; this increase in capillary pressure parallels the increase in ventricular pressure. Since this mechanism tends to maintain a constant difference in hydrostatic pressure between choroid and ventricle, the filtration pressure will be altered mainly by changes in the osmotic pressures.

The osmotic pressure of the blood under normal conditions is relatively constant, and therefore it seemed worth while to me to approach the problem by observing the effect of varying experimentally the osmotic pressure of the ventricular fluid.

METHOD

Hydrocephalic dogs were prepared in the following manner: Under ether anesthesia a midline incision was made from the occipital protuberance to the spine of the first cervical vertebra, and the muscles were separated and retracted. The margin of the occipital bone was rongeured away to expose fully the region of the fourth ventricle after opening the dura. The cerebellum was then retracted upward, and a plug of cotton soaked in a water suspension of lamp-black was introduced into the aqueduct of Sylvius. The cotton plug, acting as a physical block, is aided by a fibrinous reaction to the lamp-black irritant and produces an effective seal. After this, closure was accomplished in layers.

A trephine opening was then made about 5 cm. in front of the occipital protuberance and 1 cm. to either side of the midline for subsequent ventricular tapping. If the plug had been placed correctly, symptoms of hydrocephalus always developed in the animals within twenty-four hours. The experiments were carried out two days after the operation. Twenty-seven dogs were used, successful experimental preparations being obtained in eighteen. Of this number, nine animals were carried through the complete experimental procedure.

Experiment.—The animal was placed under ether anesthesia and a ventricular needle inserted through the trephine opening and through the dura, but before tapping the ventricle the manometer was attached so that there would be no loss of fluid. The manometer consisted simply of a very small-bore glass tube connected to the needle with a short piece of rubber tubing and a three way stopcock through which fluid was injected or withdrawn.

The manometric system was filled with isotonic salt solution, and the point of the needle was then introduced into the ventricle. Readings were taken at half minute intervals. In all the animals used, the initial pressure was greater than 350 mm. of water.

The reactions to manipulations were consistent, and the variations that occurred were quantitative and dependent on the degree of hydrocephalus. At the end of each experiment sufficient aniline dye was injected to restore the original pressure, and the brain was fixed in situ by the intravascular injection of formaldehyde. At postmortem examinations, if any extravasation of dye had occurred around the needle or through the fourth ventricle, the experiment was not considered valid. The graph reproduced here shows the results obtained in a typical experiment. Figure 2 illustrates the dilated dye-stained ventricles.

Observations.—In general, the manipulations were of two kinds: (1) alterations in volume of the ventricular fluid and (2) alterations in its salt content. The former caused only transient changes in ventricular pressure, whereas within the time limit of the experiment the latter caused permanent changes.

The initial pressure readings averaged 375 mm. of water (fig. 1). The first manipulation was the removal of 2 cc. of ventricular fluid (constituting a change in both volume and absolute salt content). This reduced the pressure to 140 mm. The osmotic tension in the fluid, however, was still the same as it had been when it supported a pressure of 375 mm. of water; as a result, there followed a restoration of fluid volume, the pressure rising to 230 mm. in eight minutes. The difference between 230 and 375 mm. indicates the loss in salt content.

The next alteration was purely volumetric—the addition of 0.5 cc. of distilled water. The change in pressure from 230 to 390 mm. was therefore transient, and the previous level of 230 mm. was approximated within eight minutes. This

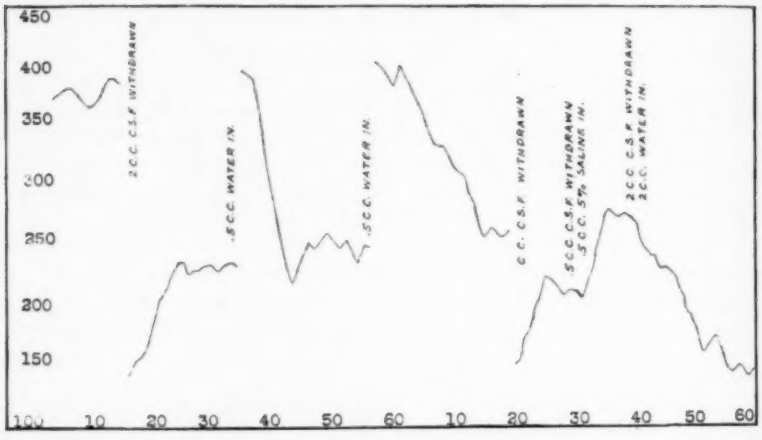


Fig. 1.—Graph of experiment 23. The ordinates represent pressure in millimeters of water; the abscissae, time in minutes.

procedure of adding distilled water was repeated with the same temporary increase of pressure, but the return to the previous level of pressure was slower (the readjustments always became slower with the prolongation of anesthesia).

The next curve in the graph represents the effect of the withdrawal of 1 cc. of fluid, and is similar to the one obtained at the beginning of the experiment. In this instance the pressure fell from 260 to 150 mm., returning to 220 mm. in five minutes.

The salt content of the fluid was then increased (without change in volume) by substituting 0.5 cc. of 5 per cent saline solution for an equal volume of ventricular fluid. The pressure then went to a higher level, increasing from 205 to 280 mm.

The process was then reversed by substituting 2 cc. of distilled water for an equal amount of ventricular fluid, and in 10 minutes the pressure fell 120 mm. from 270 to 150 mm.

It was observed that the substitution of water for cerebrospinal fluid produced a somewhat greater and more lasting lowering of pressure than that which was

attained by the simple removal of fluid. The possibility of the clinical application of this finding should be considered in cases which require spinal or ventricular tapping for relief of pressure.

COMMENT

In these experiments it was repeatedly found that as much as 15 cc. of distilled water, an amount almost equivalent to the volume of the brain, could be injected within a space of two hours; after each injection the pressure returned to the original level. Immediate postmortem

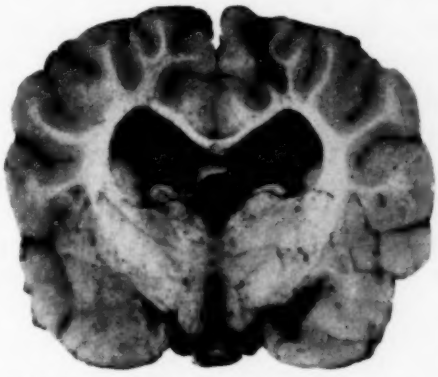


Fig. 2.—Cross-section of the brain of the animal used in experiment 23, showing the dilated, dye-stained ventricles.

Fig. 3.—Cross-section of normal dog's brain for comparison with figure 2.

examination did not show these brains to be edematous, and led to the conclusion that such rapid and complete absorption took place directly into the blood stream through the choroid plexus. On the other hand, ventricular fluid could be withdrawn repeatedly without lowering the ultimate ventricular pressure, if the salt content so withdrawn was replaced in the form of hypertonic saline solution.

In all the manipulations, alterations in the volume of fluid produced only transient effects on ventricular pressure, while alterations in the salt content of the ventricular fluid produced changes in pressure which

were permanent within the time limits of the experiment. In all the experiments the choroid plexus behaved in a manner consistent with the conception that it functions as a semipermeable membrane, permitting passage of fluid in either direction in accordance with the laws of osmosis.

CONCLUSIONS

1. In a closed ventricular system, the intraventricular pressure may be altered and to a certain extent controlled by experimentally varying the salt content of the ventricular fluid. The variations in pressure due to changes in the volume of fluid are transient, the pressure quickly reaching a level determined by the salt content.

2. The choroid plexus may act as a dialyzing membrane, permitting the passage of fluid in either direction.

THE GANGLIONEUROMAS OF THE CENTRAL NERVOUS SYSTEM*

BERNARD J. ALPERS, M.D.
AND
FRANCIS C. GRANT, M.D.
PHILADELPHIA

Among the confused group of tumors described as neuromas, one subclass stands out in well defined relief. This is the class that has been variously described as ganglioneuroma (Bailey and Cushing), ganglioglioma (Perkins) and ganglioglioneuroma (Bielschowsky). Despite the difference in conception, which seems to be indicated by the varied terminology, these tumors constitute a well defined group with well defined characteristics. They are found in the cerebrospinal nerves and ganglia, in the sympathetic system, and most rarely in the central nervous system. In the latter situation only a few such tumors have been reported. We here record a typical ganglioneuroma, the only one in a large series of cases of tumor of the brain in the series of Dr. C. H. Frazier in the University Hospital, Philadelphia.

CLASSIFICATION

The first satisfactory attempt to classify the neuromas was made by Virchow[1] who differentiated between false and true neuromas. In the former no newly formed nerve elements were usually present, while in the true neuromas they were found in varying proportions. Virchow divided the true neuromas again into myelinic forms, which were composed of nerve cells, nerve fibers and their sheaths, and amyelinic forms, consisting of nerve cells and unmedullated nerve fibers. The ganglioneuromas as now known would fall into Virchow's amyelinic true neuroma group.

A simpler classification is that which has been proposed by Pick and Bielschowsky.[2] They divided the blastomatous formations of the nerve elements into two general forms—mature and immature. The mature neuromas always assume characteristics of a ganglioneuroma

* Submitted for publication, Feb. 25, 1931.

* From the Neurosurgical Clinic and Laboratory of Dr. C. H. Frazier, University Hospital, Philadelphia.

1. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1864.

2. Pick, L., and Bielschowsky, M.: Ueber das System der Neurome und Beobachtung an einem Ganglioneurom des Gehirns nebst Untersuchung über die Genese der "Nervenfasern" in "Neurinomen," Ztschr. f. d. ges. Neurol. u. Psychiat. **6**:391, 1911.

or a ganglioglioneuroma. The immature forms include the numerous forms of neuroma which have been described in the peripheral and sympathetic nervous systems. These are the neurocytomas of Marchand, the neuroblastomas of Wright, and possibly the neurinomas of Verocay. This conception of the neuromas has the virtue of simplicity at least, and makes possible a fairly rational grouping of the numerous neuromatous tumors. The subject will be considered in detail later.

REVIEW OF LITERATURE

While ganglioneuromas have been described elsewhere in the nervous system, the brain seems to be a rare seat of these growths. Schmincke [3] seems to have been the first to give an accurate description of these tumors in the central nervous system, although Worcester [4] had previously reported a case. His first case, a tumor the size of a walnut, was found in a youth, aged 17, who had suffered from epilepsy since 8 years of age. It was located in the anterior part of the temporal lobe, from which it shelled out rather easily. Microscopically, it consisted of a network of glia cells showing amitotic division, among which were numerous apolar, unipolar and bipolar ganglion cells, often with two nuclei. These contained Nissl bodies of an atypical sort. Schmincke found in addition what he called "mother cells," arranged in a syncytium, with long, spindle-shaped nuclei. These he believed to be neuroblasts, and from them he traced all stages of development to ganglion cells.

In 1911, Pick and Bielschowsky reviewed the subject of the neuromas in detail and added a case in which the tumor was found in the medulla and upper portion of the cervical cord. This tumor consisted of a vessel-rich glial stroma in which lay numerous unmyelinated nerve fibers and ganglion cells. The glial stroma was dense in some parts and loose in others. The majority of the nerve cells appeared round, like spinal ganglion cells, while others were spindle-shaped, multipolar and pyramidal-shaped. They showed a chromatophilic and fibrillar structure of their cytoplasm, so that it was hard to believe that they were tumor cells. Dendrites and axons could be followed in some cells. Cells with two nuclei were commonly encountered. Regressive fatty changes and neuronophagia were commonly seen in the ganglion cells. The tumor contained a tremendous number of unmyelinated nerve fibers, forming rich branches and often in close relation to the blood vessels. Owing to the combination of the glia and ganglion cells, Pick and Bielschowsky suggested that these tumors be called ganglioglioneuromas.

---

3. Schmincke, A.: Beitrag zur Lehre des Ganglioneuroma, Beitr. z. path. Anat. **47**:354, 1909-1910.

4. Worcester, W. L., quoted by Courville, C. B.: Ganglioglioma, Arch. Neurol. & Psychiat. **24**:439 (Sept.) 1930.

Achucarro [5] reported a ganglioneuroma in a man, aged 21. The tumor sprang from the cerebellum and projected into the fourth ventricle. It was composed of numerous ganglion cells which were round, bipolar or, sometimes, multipolar. Most of them were round or spindle-shaped; the multipolar cells were rare. Bielschowsky's method showed axis cylinders. Nissl bodies were found, usually in small numbers, but in some cases they were present in great numbers. Multinucleated ganglion cells were found in Achucarro's case. An unusually large number of nonmyelinated fibers were present in the tumor. Connective tissue was everywhere abundant.

Schmincke [6] reported his second case in 1914. In this case also, that of a youth, aged 17, a tumor the size of a walnut was found in the anterior third of the temporal lobe. Its microscopic structure was similar to that in his first case, with many large cells, often multinucleated, of manifold form, measuring from 20 to 240 microns. Among these were smaller cells which Schmincke interpreted as younger forms of the large cells.

The base of the brain is a favorite seat of the ganglioneuromas. Robertson [7] found one of these tumors which arose apparently from the floor of the third ventricle, extended anteriorly to the olfactory nerves and posteriorly to the mammillary bodies, and was surrounded by the vessels of the circle of Willis. Its surface was lobulated, dense in one part and soft in the other. Microscopic study of the tumor showed adult ganglion cells, chiefly apolar, with Nissl substance concentrated at their periphery. Both neuroglia and nerve fibers were present in the tumors, as well as many degenerated ganglion cells. Robertson called this tumor a ganglioneuroma amyelinicum.

Berblinger [8] reported a ganglioneuroma in a girl, aged 17. It was found on the left side of the septum pellucidum. Histologically, it was composed of ganglion cells which contained no true Nissl substance but rather a chromatic granulation that was thought to be unformed Nissl bodies. Unmyelinated nerve fibers were numerous in the tumor.

---

5. Achucarro, N.: Ganglioneurom des Zentralnervensystems, Folia neurobiol. **7**:524, 1913.

6. Schmincke, A.: Ein Ganglioneurom des Grosshirns, Verhandl. d. deutsch. path. Gesellsch. **17**:537, 1914.

7. Robertson, H. E.: Ein Fall von Ganglioneurom am Boden des dritten Ventrikels mit Einbeziehung des Chiasma opticum, Virchows Arch. f. path. Anat. **220**:80, 1915.

8. Berblinger: Ganglioneurom des Gehirns, München. med. Wchnschr. **64**: 916 (July 10) 1917.

Another such tumor lying at the base of the brain was reported by Greenfield.[9] It extended from the olfactory bulbs to the anterior surface of the pons. Histologically, it was composed of two apparently different structures: large, multipolar, often multinuclear cells with a large nucleus, a clear nucleolus and darkly staining cytoplasm, and small round cells with scanty cytoplasm among which were bands of fibrous tissue. Nerve processes were found in the large and small cells. There was no evidence of myelin formation and no trace of a true Nissl substance within the cells.

In Olivecrona's [10] cases both the tumors were in the cerebral hemispheres. In his first case, that of a man, aged 39, a mass 7 cm. long and 6 cm. in diameter was found in the right parietal lobe. The tumor was composed of large cells with round or oval form, with one or more nuclei and with homogeneous cytoplasm. Multipolar forms, considered to be malformed nerve cells of Golgi type II, were seen. The stroma was composed of both myelinated and unmyelinated nerve fibers and fibrous tissue, among which were numerous cells thought to be cells of the sheath of Schwann. His second case demonstrated a ganglioneuroma in the inferior part of the right frontal lobe, extending across to the left frontal lobe. Histologically, the tumor was composed of large round or polyhedral cells with one or more nuclei. Nissl bodies were not found. Numerous glia cells were present in the tumor. The stroma was composed of connective tissue, unmyelinated nerve fibers and glia fibers.

Lhermitte and Duclos [11] reported a ganglioneuroma of the cerebellum in a man, aged 36. At necropsy there was only a hypertrophy of the convolutions of the left cerebellar hemisphere. Histologically, this hypertrophied area consisted of two portions: an outer zone of nerve fibers and an inner zone of nerve cells with Nissl substance.

Josephy [12] described a tumor lying at the base of the brain which he called a "central neurinoma," following the suggestion of Verocay. This tumor has been classified by Bailey and Cushing as a spongioblastoma unipolare. I had the good fortune to see Professor Josephy's preparations in Hamburg in the latter part of 1929. The tumor, an infiltrating growth at the base of the brain, extended from the cerebellum to the thalamus, and was composed almost entirely of large, multipolar, multi-

9. Greenfield, J. G.: The Pathological Examination of Forty Intracranial Neoplasms, Brain **42**:29, 1919.

10. Olivecrona, H.: Zwei Ganglioneurome des Grosshirns, Virchows Arch. f. path. Anat. **225**:1, 1919.

11. Lhermitte, J., and Duclos: Sur un ganglioneurome diffus du cortex du cervelet, Bull. de l'Assoc. franç. p. l'étude du cancer **9**:99 (April 19) 1920.

12. Josephy, H.: Ein Fall von Porobulbie und solitärem zentralen Neurinom, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:62, 1924.

nucleated cells of the ganglion cell type. I believe that this tumor is in reality a ganglioneuroma, but that it has been classed as a central neurinoma by Josephy in order to make it conform to the views expounded by Verocay.

Similarly, the tumor reported by McPherson [13] may justifiably be classed as a ganglioneuroma.

Perkins' [14] case was that of a boy, aged 16, who had a firm, hard tumor in the floor of the third ventricle, causing an internal hydrocephalus by blockage of the iter. Microscopic study located islands of large cells separated by much fibrous-like tissue. The cells varied from 8 or 10 to 40 microns in diameter. Many of them contained two nuclei, and often there were as many as 8 or 9 in a single cell. The nuclei resembled those of nerve cells, and often they possessed two nucleoli. The matrix of the tumor was composed of a large amount of fibrous-like tissue in which there were no collagen, or elastic fibers, and no myelinated fibers. Perkins concluded that "it is hard to say just what this matrix represents. It resembled neuroglia tissue, and it is possible that the specificity for this stain had not developed; that is, these fibers may be embryonic neuroglial fibers or young connective tissue fibrillae."

A ganglioneuroma in the infundibular region in a woman, aged 40, has recently been described by Marinesco.[15] The growth was the size of a pigeon's egg, and was united with the right hippocampal gyrus. The tumor was composed largely of atypical ganglion cells which lay in a relatively cell-rich glial stroma. Numerous processes emanated from the cells. These were thick in the larger cells and very slender in the smaller ones, forming dense bundles of fibers which compressed the hippocampal gyrus. Unmyelinated nerve fibers were present, but these never penetrated into the adjacent cortex. The ganglion cells were chiefly apolar, but some multipolar elements were present. Atypical Nissl substance was seen in the cytoplasm, and neurofibrils were demonstrated.

Paul [16] found a ganglioglioneuroma, the size of a walnut, in the vermis of the cerebellum of a child, aged 5¾ years. The tumor was clearly differentiated from the surrounding tissue, and was firm and grayish red. It was made up largely of ganglion cells of an immature form without neurofibrils but with Nissl substance in the cytoplasm around the nucleus. Numerous monster giant cell forms, with many satellite cells and with evidence of neuronophagia, were encountered.

13. McPherson, D. J.: Studien über den Bau und die Lokalisation der Gliom, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **27**:123, 1925.

14. Perkins, Orman C.: Ganglioglioma, Arch. Path. **2**:11 (July) 1926.

15. Marinesco, G.: Sur un cyto-neurome de la region infundibulaire (ganglioneurome), Ann. de méd. **20**:577 (Dec.) 1926.

16. Paul, Fritz: Beitrag zur Histopathologie der Ganglioneurom, Beitr. z. path. Anat. u. z. allg. Path. **75**:221, 1926.

The stroma was made up largely of connective tissue, with some neuroglia fibers and scattered nerve fibers in the tumor. Mitoses and amitoses were encountered. No myelin-covered fibers were present. Paul suggested the term ganglioglioblastoma to designate these tumors.

Two recent cases of ganglioneuroma of the central nervous system have been added to this scanty list by Bielschowsky and Henneberg.[17] Their first case was that of a girl, aged 16, who had a tumor in the infundibular region but without any connection with the hypophysis. It lay between the cerebral peduncles and the medial surface of the cornu ammonis, compressed the fornix and formed a cyst in the brain. It was found to arise, not from the infundibular area, but from the dorsal wall of the left inferior horn of the lateral ventricle. It consisted of two histologically different parts connected by a transition zone. The tumor had an alveolar structure in the spaces of which lay ganglion cells either singly or in groups. Their nuclei were pale; they had a central nucleolus, and axons and dendrites. Often, glial satellites could be seen around them. Regressive changes could be seen within them. The stroma consisted of a mixture of glia and connective tissue fibers, among which were numerous thick-walled vessels.

The second case of Bielschowsky and Henneberg was that of a girl, aged 11, who had a tumor in the right temporal lobe lying between the gyri hippocampi and fusiformis. The cornu ammonis, subiculum and the greater part of the presubiculum were intact. Of the gyrus hippocampi only the lateral third of its basilar surface was involved by the tumor. The tumor consisted of two portions, a dense fibrous zone adherent to the pia, among which were islands of ganglion cells, nerve fibers and glial elements, and another zone in which fibrous elements were not prominent, but in which glial elements formed the chief mass. The ganglion cells showed many highly differentiated forms with a well defined axon and neurofibrils. Bipolar forms with gyrochrome arrangement of the chromatin resembled sympathetic ganglion cells. Numerous immature and regressive forms were present in the tumor. Glia cells were present in abundance in parts of the tumor. Bielschowsky and Henneberg urged the correctness of their term, ganglioglioneuromas, for these tumors.

Courville[18] recently reopened the entire question of the ganglioneuromas and reported two well studied cases specifically impregnated by the newer silver methods. His first case was that of a girl, aged

17. Bielschowsky, M., and Henneberg, R.: Ueber Bau und Histogenese der zentralen Ganglioglioneurome, Monatschr. f. Psychiat. u. Neurol. **68**:21 (March) 1928.

18. Courville, Cyril B.: Ganglioglioma, Arch. Neurol. & Psychiat. **24**:439 (Sept.) 1930.

15, who had a small firm tumor arising from the tuber cinereum and lying between the optic chiasm and the mammillary bodies. This tumor was continuous with another small mass which projected into a large cystic cavity in the left hemisphere. Histologically, the tumor contained numerous neuroblasts and ganglion cells. The former were present in apolar, bipolar and multipolar forms. The ganglion cells possessed one or more processes, which were traceable for some distance. They contained atypical Nissl substance in their cytoplasm. The nuclei were large and vesicular, and sometimes multiple. Degenerated forms were present. The nerve fibers in the tumor were all unmyelinated; no myelinated fibers were seen. Spongioblasts were found. Connective tissue and blood vessels were present in moderate amounts.

Courville's second case consisted of a minute ganglioneuroma in the region of the tuber cinereum. It measured from 1 to 2 mm. in diameter and lay to the left of the infundibulum. Microscopically, the tumor contained various types of cells in a loose stroma. The most conspicuous element was a large round unipolar or bipolar cell containing one or two vesicular nuclei. A sort of Nissl substance was present in the cytoplasm, and occasionally neurofibrils were present. Degenerated forms were seen. Neuroblasts were seen. Large numbers of glia fibers were present, also fibrillary astrocytes.

Wätjen [19] found a ganglioneuroma in the right parietal lobe, extending into the frontal and temporal lobes. The tumor contained nerve cells and fibers, and glia cells and fibers. The histologic feature of greatest interest was found in the huge cells (similar to those found in Paul's case), often reaching 400 microns in size, with multiple nuclei but without neurofibrils or Nissl substance. They often showed evidence of degenerative changes, and Wätjen looked on them as ganglion cells which had assumed a blastomatous character.

Multiple malignant ganglioneuromas have been reported in the tumors of this type found in the peripheral nervous system, but none was recorded in the central nervous system until the case of Bielschowsky.[20] This was the case of a man, aged 26, who had a tumor in the cerebellopontile angle and several elevations as large as a lentil under the ependyma. Microscopically, there were many more small tumors than could be detected grossly. The tumor possessed two layers—superficial and deep. In the deeper layers were numerous cells of neuroblastic origin in various stages of maturity, in addition to mature ganglion cells among which was a net of nerve fibers. The superficial layer consisted almost entirely of glial tissue.

19. Wätjen, J.: Ein Ganglioglioneurom des Zentralnervensystem, Virchows Arch. f. path. Anat. **277**:441 (May) 1930.

20. Bielschowsky, M.: Das multiple Ganglioneurom des Gehirns und seine Entstehung, Jahrb. f. Psychol. u. Neurol. **32**:1, 1925.

REPORT OF CASE

Ganglioneuroma at the base of the brain. Duration of illness about five years. Signs indicating localization in the sellar region; partial removal of the tumor. Death.

History.—A. G., a boy, aged 16, entered the University Hospital in November, 1929, on the service of Dr. C. H. Frazier. His illness had started four years previously with headaches in the frontal region radiating throughout the head. These

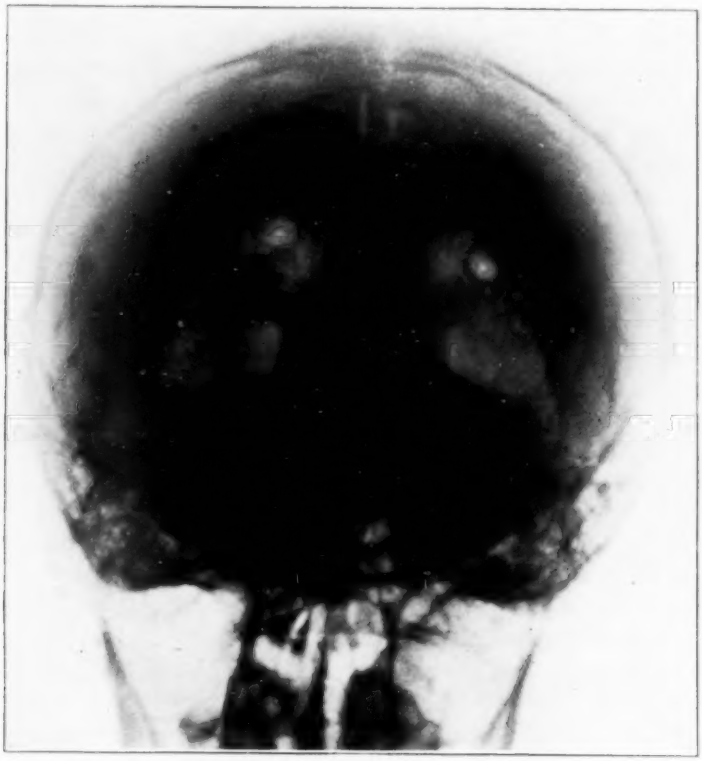


Fig. 1.—Ventriculogram showing the total lack of filling of the third ventricle.

attacks first occurred at intervals of two or three days, only to be succeeded by similar attacks every morning and evening. At times the headaches were accompanied by nausea and vomiting. After being fitted for glasses the headaches improved, until four or five weeks before entrance when they increased both in frequency and severity. At the time of entrance to the hospital, he began to have difficulty in vision. At first, print seemed blurred, but at the time of entrance he could not see to read. During the two weeks before entrance into the hospital he had frequent attacks of complete blindness lasting for a minute or two. Following these he recovered sight enough to make out objects. At the time of entrance into the hospital he could not see enough to walk about.

Neurologic Examination.—There was slightly decreased perception of odors on the left side. The patient had no vision at all in the right eye, and had light perception only in the center of the field of the left eye. The pupils were regular and dilated, and reacted neither to light nor in accommodation; the consensual reflex was gone. There was weakness of the left abducens. The other cranial nerves were normal. He showed rather marked incoordination with either leg, and swayed in the Romberg position. There was no weakness of the extremities. Sensation was intact. The tendon reflexes were all diminished except for a normal right patellar and achilles reflex. The cutaneous reflexes were intact. From the endocrine standpoint, he showed soft, smooth skin, hips of the feminine type, a

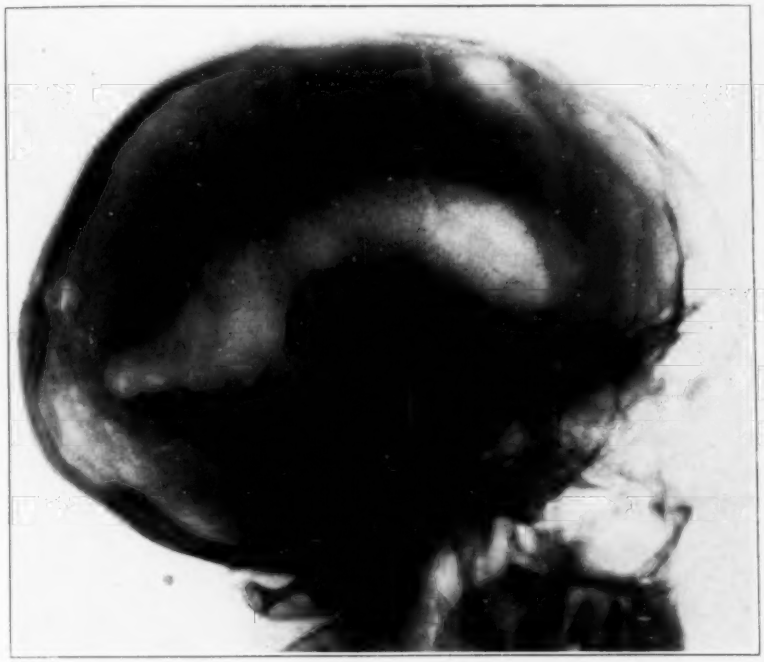


Fig. 2.—A lateral view demonstrating the practically complete occlusion of the third ventricle.

feminine distribution of pubic hair, very little axillary hair and rather prominent breasts. Ophthalmoscopic examination revealed 5 diopters of choking in each eye.

Laboratory Studies.—Roentgen studies revealed a marked atrophy of the dorsum sellae, some enlargement of the pituitary fossa, some erosion of the sellar floor and an encroachment of the sphenoid sinuses.

Examinations of the spinal fluid gave evidence of an increased pressure. The water manometer read 640 mm. of pressure; the cell count was 6, and the protein content 3 units. The Wassermann reaction of the blood was negative.

Owing to the confused picture presented by all the evidence, it was decided to perform a ventriculography in order better to localize the tumor. Methylene blue (methylthionine chloride, U. S. P.) introduced into the right ventricle failed to appear in the left. Both ventricles were very large, containing 150 cc. of fluid.

The xy-ray plates showed a complete obliteration of the third ventricles and a failure of communication between the lateral ventricles.

Operation.—On the basis of the studies, Dr. Grant performed a right transfrontal craniotomy and disclosed a tumor in the pituitary region. Its surface was covered by a great many blood vessels, and the right trigeminal nerve seemed particularly involved in it. The tumor was solid and encapsulated. A portion of it was removed. However, hyperthermia developed on the day after the operation, and the patient died.

Microscopic Examination.—Only a small amount of material was available for study so that great economy had to be exercised in its use. The following

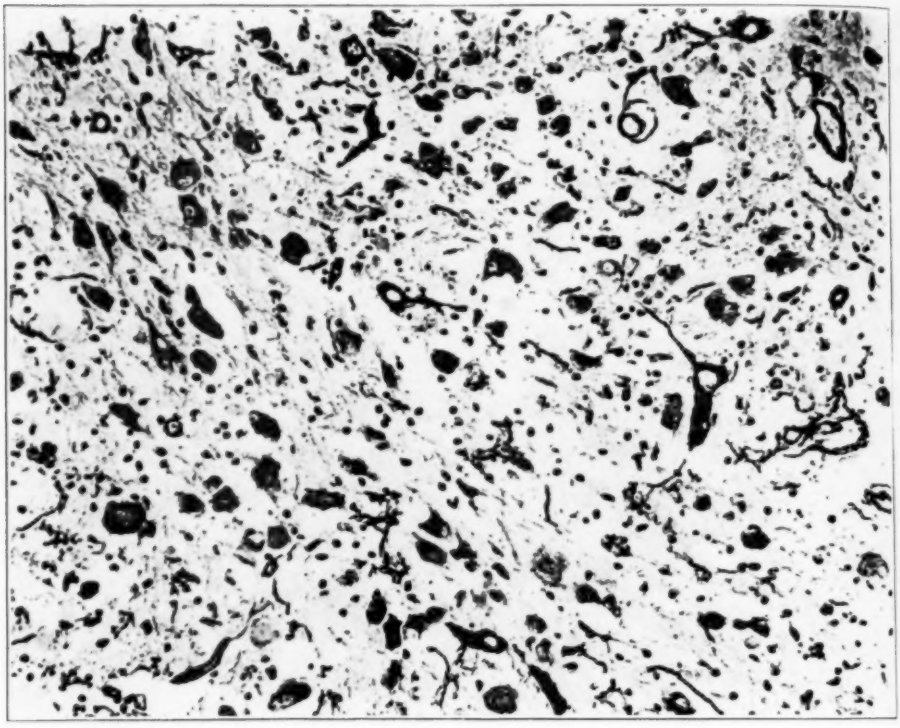


Fig. 3.—Ganglion cells within the tumor. Perdrau stain; × 205.

methods were utilized: hematoxylin and eosin, van Gieson, aniline blue, hemalum and eosin, phosphotungstic acid-hematoxylin, Perdrau, Bielschowsky-Plein for Nissl bodies, Bielschowsky's method in section and block for neurofibrils and axis cylinders, the Gross modification of this method, Schultze's method for axis cylinders, Hortega's first variant for centrosome structures, and several other silver carbonate methods of del Rio-Hortega for the impregnation of the cells, connective tissue and nerve fibers. Since the tissue had been fixed only in formaldehyde and formaldehyde-bromide, the original Cajal method for neuroblasts could not be used, but a modification was devised which gave good results.

General Description of Tumor: The tumor was surrounded by a thin, fibrous capsule. It was cellular. Its most striking feature lay in the large cells which

were scattered throughout the specimen. Often these cells lay in groups, but for the most part they were scattered diffusely throughout the specimen. Sometimes there was a clearly defined tendency for them to gather in groups of two, three or more cells. Occasionally they lay in close proximity to a vessel, but never in a pseudorosette formation. The relationship was one of proximity and not of a definite architectural relationship to the vessels.

Scattered among the large cells were numerous small cells which lay in a fibrillar, loose-meshed carpet. Some areas of the tumor were composed almost entirely of these smaller elements. Here they formed a fairly dense structure,

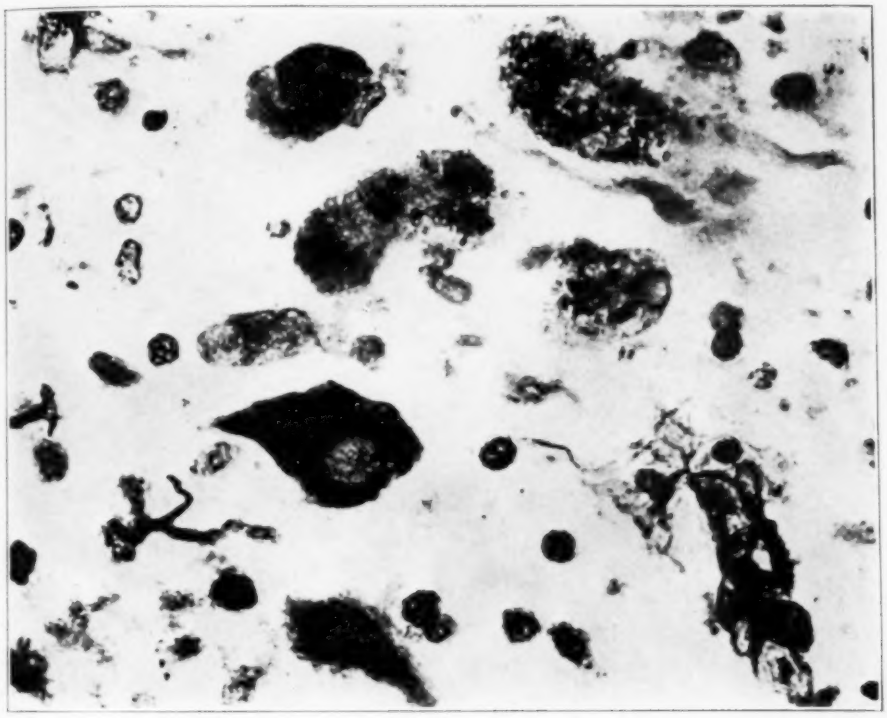


Fig. 4.—A group of ganglion cells, most of them apolar, but with one unipolar cell. Bielschowsky stain; × 875.

while in the regions in which the larger cells predominated they were much less numerous.

The tumor was vascular, and the blood vessels were fairly numerous. A few of them were large arterioles, but most of them were venules and large capillary spaces. Many of these were filled with blood. In many places the walls of the vessels were infiltrated with inflammatory elements; these were present also in the perivascular spaces; they consisted of large mononuclear elements, among which were scattered polynuclear cells.

The connective tissue stroma was very scanty. With the van Gieson stain, no collagen was seen. There was connective tissue around the vessels as seen by

Mallory's aniline blue stain, but it did not penetrate into the tumor. It was confined strictly to the vicinity of the vessels.

The large cells were undoubtedly ganglion cells. In some regions they were much more plentiful than in others, but on the whole they were very numerous throughout the tumor. They varied in size from 20 to 40 microns. Some were small, while others were very large and appeared much like giant cells on superficial inspection.

The cytoplasm of the large ganglion cells was arranged in large masses. The shape varied considerably with the usual aniline dye stains. Often they were round, having an elliptical or roughly oval appearance. In rare instances the

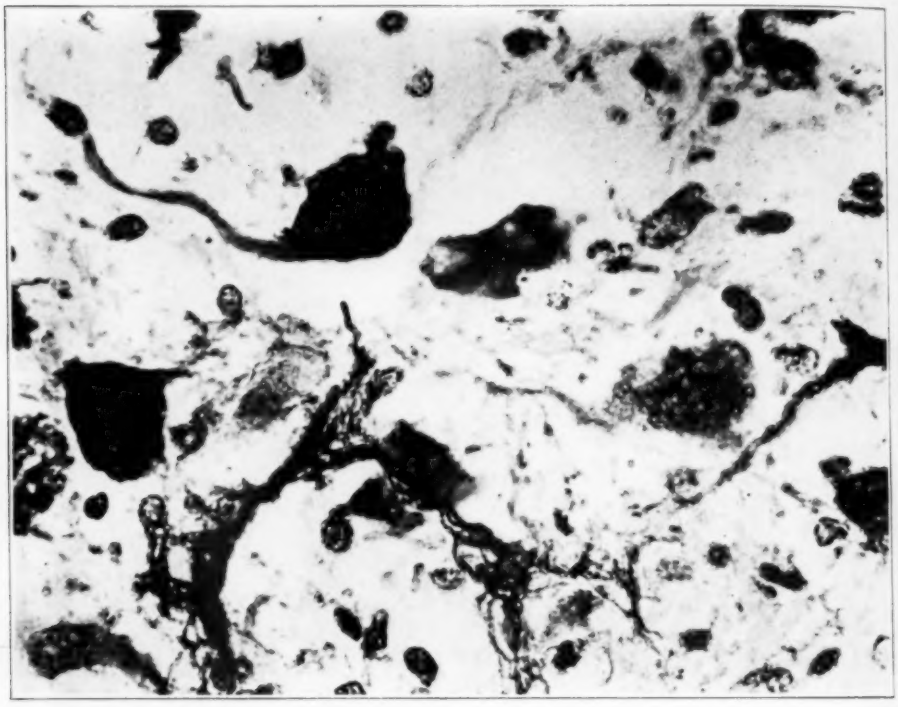


Fig. 5.—A group of ganglion cells with one unipolar cell clearly seen. Bielschowsky stain; × 875.

hematoxylin-eosin stain showed one of these cells as a large bipolar structure with two large processes streaming away from it. Sometimes the cytoplasm assumed extremely bizarre, irregular shapes. Usually it had a smooth, homogeneous appearance, but sometimes it appeared coarsely granular, the granules staining a refractile pink with eosin.

With the silver stains the cytoplasm of the cells stood out clearly. Most of the cells were round, without processes, and appeared like the cells of a sympathetic ganglion. Some cells possessed a single process which was thick at its cellular end and tapered off rapidly to a rather fine termination. Bipolar cells were also present, but were relatively few in number; here there was a single process which left each

pole of the cell. Of the two processes, one tapered off as in the unipolar cell, while the other persisted as a thick, stubby prolongation. Occasionally, branching of a process could be seen. Multipolar cells were sometimes found, but these were rarest of all. The most suitable silver method for demonstrating the nerve cells was that of Schultze-Stöhr. By this the cells were well impregnated. They were found to consist for the most part of apolar ganglion cells, with many unipolar, bipolar and multipolar forms. A good many of the smaller cells which were seen in the tumor were found also to be ganglion cells of a somewhat lesser stature than their larger neighbors.

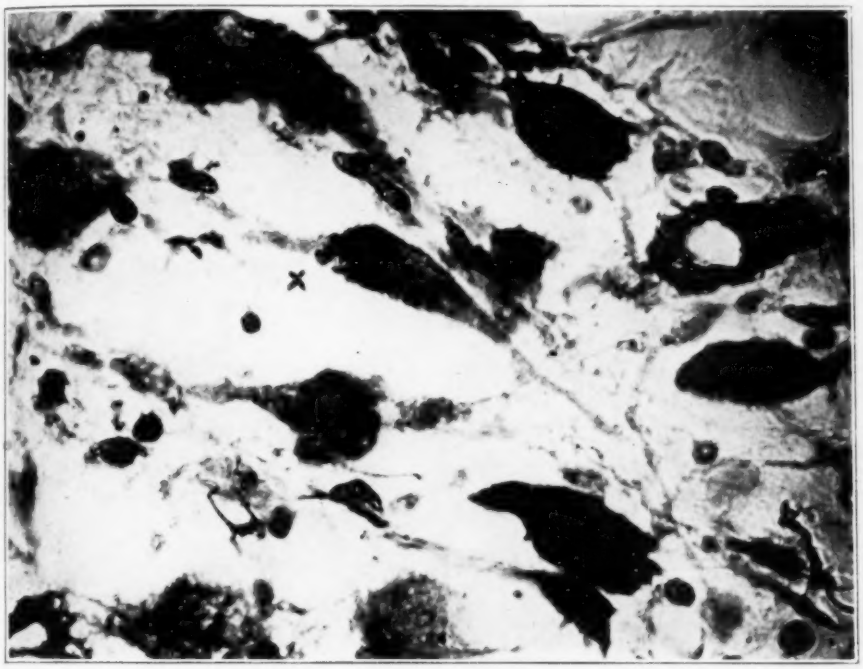


Fig. 6.—A group of ganglion cells with a bipolar cell at *x*. Bielschowsky stain; × 875.

In most of the ganglion cells no neurofibrils could be demonstrated within the cytoplasm by the Bielschowsky method or any of its modifications. In a few of the bipolar and multipolar cells fine silver fibrillae could be seen at the periphery of the cell, extending for a short distance into one of the processes. None of the cells contained the rich content of neurofibrils seen in normal ganglion cells. Myelin sheath stains showed no myelinated nerve fibers.

Nerve fibers were readily demonstrated by the Schultze-Stöhr method. They formed a thick feltwork throughout the tumor. Most of them were unmyelinated. Similar fibers were seen by Bielschowsky's and Hortega's methods. By means of Cajal's method for unmyelinated nerve fibers, a thick feltwork of these was seen in the tumor; they were more marked in some parts than in others.

No myelinated nerve fibers were demonstrated by either the Weigert or Kulschitsky method. The cytoplasm contained no well defined chromidial substance corresponding to Nissl bodies as seen with the Bielschowsky-Plein stain. It appeared as a homogeneous, more or less vacuolated mass. Sometimes fine, dark blue granules were visible within the cytoplasm, usually at the periphery of the cell. Occasionally, large chromatic clumps resembling Nissl bodies could be made out, but these were rare. They were extremely ill defined, and did not possess the appearance of the normal Nissl bodies.

Both the ganglion cells and the small cells contained well defined centrosomes. In the ganglion cells these were usually placed at the periphery of the cytoplasm

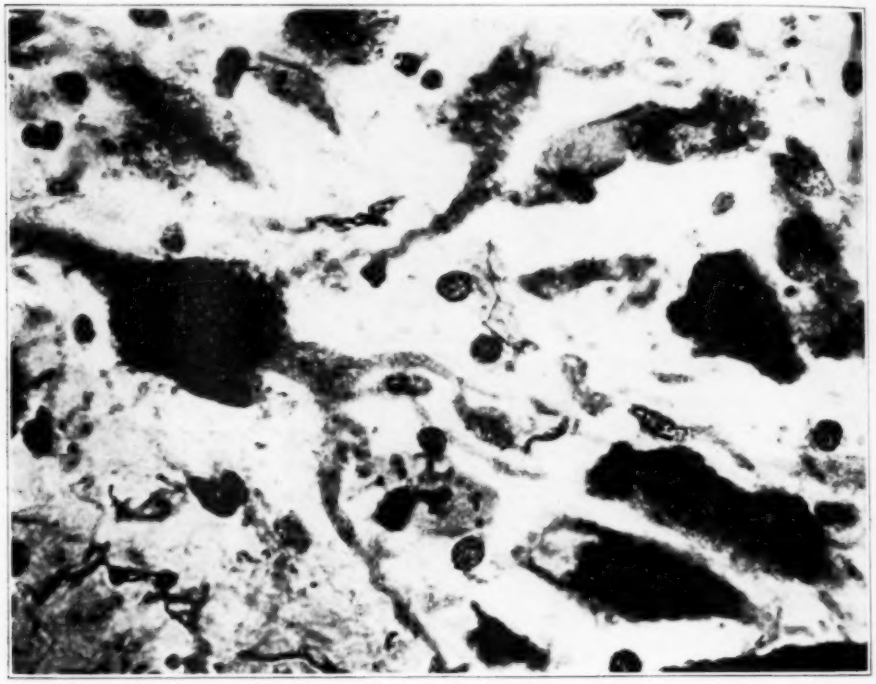


Fig. 7.—A large multipolar cell and a group of apolar cells. Note the total absence of neurofibrils. Bielschowsky stain; × 875.

where they appeared as two small dots surrounded by a refractile halo. Sometimes the centrosome was multiple, and occasionally it assumed a rodlike or whirled form. In the small cells the centrosome lay close to the nucleus. In the ganglion cells the centrosome lay parallel to the edge of the cytoplasm.

The nuclei of the ganglion cells varied in shape and size. Most of them were round, and all contained a well defined membrane. Some were oval and even crescentic in shape, and some were kidney-shaped. Practically all the nuclei possessed a large, centrally placed nucleolus which stained blue with hematoxylin. In some nuclei the nucleolus lay peripherally, close to the nuclear membrane. The nuclear chromatin was very finely granular, almost powdery, giving the entire nucleus a light vesicular appearance. The result was that the dark nucleolus stood

out sharply against a light nuclear background. The nucleus was on the whole large. It was excentrically placed in practically all the cells. It was usually at one pole of the cell, but in some instances it approached the center. Some nuclei were pyknotic. In by far the great majority of instances there was only a single nucleus in each cell, but rarely one saw two nuclei, and extremely rarely as many as three nuclei were visible. Sometimes two nucleoli were seen. Usually the nucleoli stained an intense blue, but sometimes they took a metachromatic violet tint.

In some areas of the tumor neuroglia fibrillae were extremely thick. In these regions the small cells predominated, and ganglion cells were either extremely few

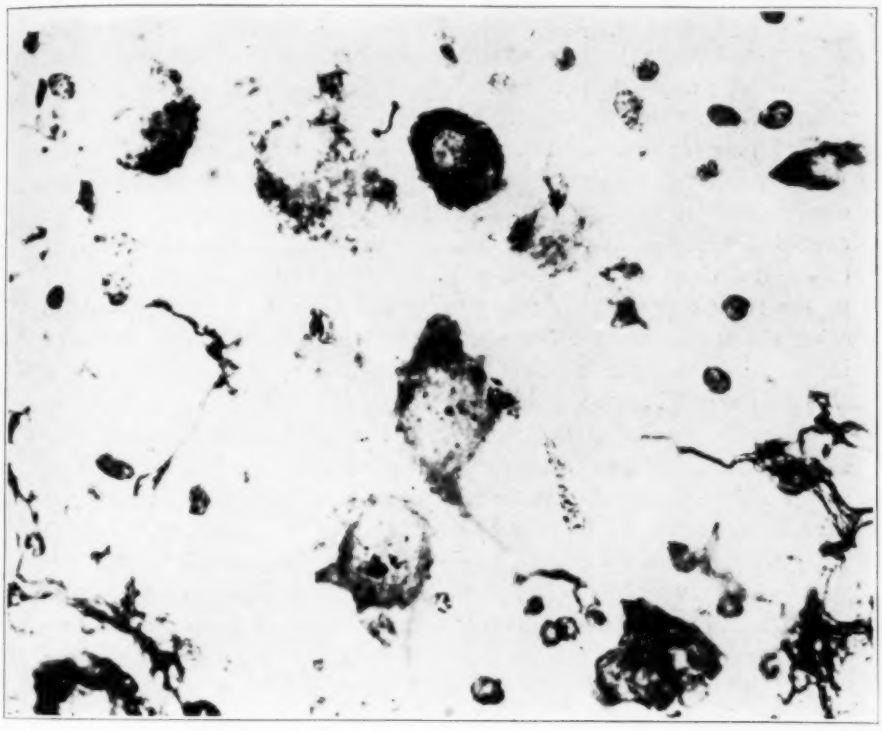


Fig. 8.—A group of ganglion cells showing evidences of degeneration. Hematoxylin-eosin; × 875.

or were absent altogether. Only scattered fibrils were seen among the ganglion cells. The fibrillae appeared as long, sweeping threads, some of them thick, which often extended over several fields. They were often arranged in bundles. Frequently they were tortuous and had a cork-screw appearance. They tended to remain independent, but sometimes they intertwined. No collaterals were anywhere visible on these fibrils, and none of them had the appearance of fibrous strands.

Degenerative changes were present in many of the ganglion cells. Some were markedly swollen, with absent nucleus and with cytoplasm containing numerous large vacuoles. Others contained many small vacuoles in their cytoplasm.

GENERAL CLINICAL AND PATHOLOGIC ASPECTS OF GANGLIONEUROMAS

Twenty-one reported cases of ganglioneuroma involving the central nervous system have been found. To these has been added a case of our own which makes twenty-two reported cases of these tumors in the brain; twelve have been found at the base of the brain, and nine in the cerebral hemispheres. Of those at the base, four were identified definitely as arising from the floor of the third ventricle, (Robertson, Greenfield, Perkins and Courville); three were found in the infundibular region (Marinesco, Bielschowsky, and Henneberg, Alpers and Grant); two involved the cerebellum (Achucarro and Lhermitte); one involved the medulla (Pick and Bielschowsky); one was found in the cerebellopontile angle (Bielschowsky), and one case, that of Josephy, infiltrated the brain stem from cerebellum to thalamus. It is an extremely interesting fact that of the ganglioneuromas in the cerebrum the majority were found in relation to the temporal lobe. In one of Schmincke's cases the tumor was located in the anterior half of the left temporal lobe; in the other case it was in the anterior half of the right temporal lobe; in one of Bielschowsky and Henneberg's cases the tumor was in the right temporal lobe, and in the case of Dumas, in the right cerebral hemisphere. The significance of this observation will be discussed later.

There is no characteristic picture that serves to distinguish a ganglioneuroma from any other extrasellar tumor. Certain clinical facts, however, are clear. Among nineteen cases with clinical records ten were in females and nine in males. The age incidence varied from 11 to 40 years, and the average age was slightly over 20 years. The ganglioneuroma is therefore much more common in young persons and is found equally in males and females, possibly a little more frequently in the latter. The symptoms that such a tumor may cause vary with its extent. Pressure symptoms are present but not marked. Pituitary symptoms are frequently observed, due possibly to compression of the hypophysis. They may dominate the clinical picture, as in our case. In Greenfield's case acromegaly was the outstanding clinical feature. The dorsum sellae is often atrophied, and the sella somewhat enlarged. Convulsions have been observed in many cases, but the mechanism of their production is not wholly clear. Indeed, one is struck by the number of these cases with a history of epilepsy. The diagnosis of these tumors remains a pathologic one. They are suprasellar tumors, causing mild symptoms of pressure, visual disturbances due to choked disk and atrophy, some enlargement of the pituitary fossa, and a rather varied clinical picture which is often dominated by a pituitary syndrome and convulsions.

Tumors, both in the cerebrum and at the base of the brain have been described as encapsulated. In Schmincke's first case the tumor shelled out easily from the anterior half of the temporal lobe. In his second case the tumor also appeared well demarcated from the brain substance. On the other hand, in the case of Bielschowsky and Henneberg the tumor appeared to infiltrate the brain substance and was firmly adherent to the pia mater.

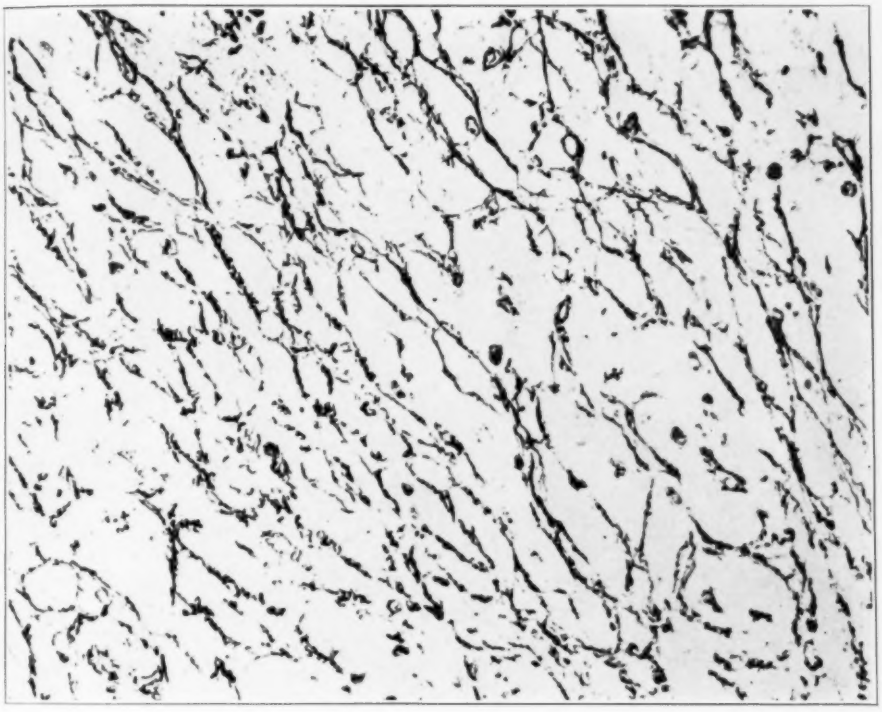


Fig. 9.—The rich network of reticulin and collagen is clearly shown. Perdrau; × 205.

The tumors at the base of the brain have usually presented a nodular or lobulated surface, projecting beyond the confines of the brain substance, and with an apparent capsule. In practically every case, however, it has been possible to find a connection with the brain substance, indicating that fundamentally the tumors are infiltrating. The tumor in Robertson's case presented itself in the infundibular region, but was found to infiltrate the floor of the third ventricle. In Perkins' case there was a very firm, hard tumor which projected as an encapsulated mass through the floor of the third ventricle, but which was

followed posteriorly into the tegmentum of the brain stem, involving the anterior part of the nucleus ruber bilaterally, passing vertically through the substantia nigra and even encroaching on the cerebral peduncles. In Marinesco's case the tumor presented itself in the infundibular region, but was found to be united with the right gyrus hippocampi. While the case of Bielschowsky and Henneberg showed a tumor between the cerebral peduncles, it was found to infiltrate into the white matter of the brain where it formed a cyst which was surrounded by an easily detachable membrane. In the case of Pick and Bielschowsky, in the medulla, and in that of Josephy, at the base of the brain, the tumors were definitely infiltrating throughout their course.

While, therefore, tumors in most instances present an extramedullary mass which appears encapsulated and enucleable, they are found when studied more closely to infiltrate the brain substance, and to be in reality infiltrating growths. Some of them in fact are entirely infiltrating, with no surface presentation whatever (Pick and Bielschowsky, and Josephy). Many of them are cystic and the cysts are filled with a clear white fluid. These cysts are large, but there are often found, in addition to these, very small cysts which are probably degenerative. Degeneration, however, is not a characteristic feature of these tumors. They are firm and well preserved as a class.

The size of the tumors has been fairly uniform. Usually they do not attain very great size, but most of them, lying at the base of the brain as they do, compress vital structures. They have been described as being from the size of a pigeon's egg (Marinesco, Bielschowsky), to the size of a walnut (Schmincke). They have reached from the optic chiasm to the pes pedunculi (Bielschowsky and Henneberg), from the olfactory nerves to the corpora mammillaria (Robertson), and from the olfactory bulbs to the anterio-inferior surface of the pons (Greenfield).

THE HISTOLOGIC STRUCTURE OF THE CEREBRAL GANGLIONEUROMAS

Despite minor variations, these tumors present a rather uniform histologic structure. They are composed of ganglion cells in varying numbers and different stages of development, of neuroglia cells and fibers, and, in some instances, of nerve fibers which are usually unmyelinated. Fibrous tissue and reticulin is present in varying amounts.

The ganglion cells constitute the most striking portion of the tumor. Some tumors are composed almost entirely of immature cells, but others may possess all the characteristics of adult cells of this type. Indeed, a few cases have been recorded in which almost the entire tumor was composed of fully matured ganglion cells. Such was the second case recorded by Bielschowsky and Henneberg. This tumor was composed of many multipolar cells with typical nuclei, with characteristic chromidial substance in the cytoplasm and with a typical

neurofibrillar structure. They were said to resemble the large cells of the motor cortex in their make-up. Bipolar cells and immature forms were also present. The tumor in the case reported by Pick and Bielschowsky was composed chiefly of ganglion cell elements, which resembled sympathetic ganglion cells, and a few which showed dendrites and axons in some instances. Most of the cells contained chromidial substance and neurofibrils in the cytoplasm. Unmyelinated fibers were present in tremendous numbers.

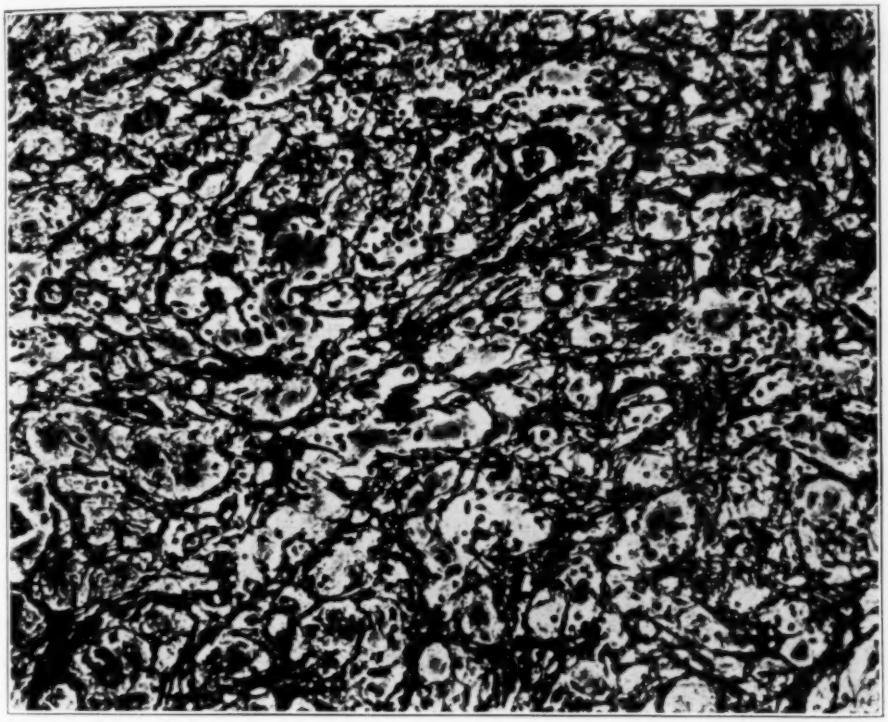


Fig. 10.—The dense connective tissue net is evident. Silver method of del Rio-Hortega; × 205.

In most of the instances recorded the majority of the ganglion cells fall short of complete maturity. The bipolar or multipolar elements may possess typical nuclei and characteristic chromidial substance but may be lacking in neurofibrils (Schmincke, Robertson, Marinesco), or they may be multipolar cells with typical nucleus and processes, but with no Nissl substance (Greenfield). Most of the cells contain a single nucleus, but some are multinuclear. The number of the nuclei varies in these instances from two to four. There are rarely more than four nuclei.

Unmyelinated nerve fibers have been found in great numbers in one tumor (Pick and Bielschowsky) and in moderate numbers in others (Marinesco, Robertson). Myelinated fibers have not been seen.

The small or nonganglion cells found in the tumors have usually been described as neuroglia cells. While no specific impregnation of the neuroglial elements has been made, a typical network of neuroglia fibers has been described in the tumors of Pick and Bielschowsky, Marinesco, Bielschowsky and Henneberg, and Robertson. Perkins could not be certain that the fibrillae which he saw in his tumor were true neuroglia fibrillae, though he suspected that they were embryonic forms of this structure. The majority of the smaller cells in the tumor are probably neuroglia cells, but some of them are small nerve cell elements. This was seen clearly in some of our silver preparations.

Our tumor was composed of numerous ganglion cells which were for the most part apolar, but among which were numerous bipolar, and a few multipolar elements. Many cells resembled sympathetic ganglion cells. In only a few instances was anything resembling chromidial substance found in the cytoplasm, and neurofibrils were extremely rarely seen in the ganglion cells. Unmyelinated nerve fibers were abundant, and nests of neuroglia fibrillae were present in some parts of the tumor. Myelinated nerve fibers could not be demonstrated. The small elements were not impregnated by Cajal's method for demonstrating neuroblasts, nor could they be impregnated by specific methods for neuroglia. Nevertheless, the presence of neuroglia fibrillae usually among these cells is presumptive evidence that these are probably neuroglial elements. A connective tissue stroma could not be seen throughout the tumor, but was found in mild degree about the vessels. Reticulin was found scattered throughout the tumor. The tumor was of slow growth. No mitoses were found.

THE HISTOGENESIS OF THE GANGLIONEUROMAS

The ganglioneuromas may spring from any part of the cerebral hemispheres, but particularly from the temporal portions, from the cerebellum, the medulla and upper cervical cord, and from the base of the brain, notably the diencephalic region. It is obviously difficult therefore to find a key which will unlock the mystery enshrouding these varied seats of origin. Of all the possible loci from which they may arise, these tumors prefer the region of the diencephalon. They have been found here in eight of twenty instances. In all but one of these cases the tumor arose from the floor of the diencephalic region. In all probability the ganglioneuromas of this area arise as the result of tumor-developing tendencies of groups of cells in the floor plate of the diencephalon during embryonic development. More rarely the cells of

the roof plate assume such properties. It is more probable that the floor plate is responsible for these cells rather than the basal plate of the diencephalon since the latter gives rise to no important nuclei in this region.

Ganglioneuromas in the cerebral hemispheres and cerebellum are probably derived also from ganglion cells which assume neoplastic properties. Except for the occurrence of these tumors more frequently in the temporal lobe, there is nothing striking in their cerebral locali-

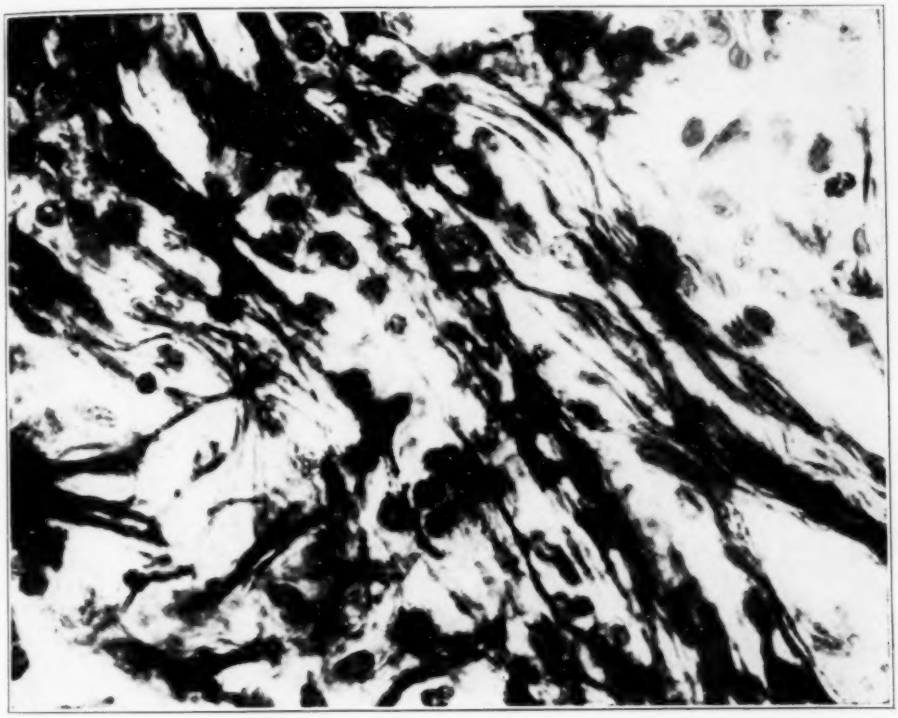


Fig. 11.—A group of nerve fibers in the tumor; Schultze-Stöhr method; × 875.

zation. In four instances the tumors were found in the temporal lobe. We believe that there may be some relationship between the occurrence of these tumors in the temporal region and their presence in the diencephalon. It is known that the tela chorioidea of the third ventricle roofs over the median portion of the telencephalon and is folded laterally into the hemispheres as the choroid plexus of the lateral ventricles. It seems possible, therefore, that in the ingrowth of this tela some aberrant ganglion cells may be carried over from the roof plate, to become lodged in the temporal lobe of one side. This seems all the more probable since the roof plate at its attachment to the alar

plates forms the habenular ganglion, which could serve as the source of origin of these aberrant cells that later assume neoplastic properties.

It is not entirely certain that the ganglioneuromas represent true blastoma formations. Some have suggested that they are really congenital malformations. Some of the instances reported have suggested the plausibility of the second possibility (Pick and Bielschowsky and Courville's second case). The immaturity of the cells, the presence of unusual forms, such as multinucleated cells, and the abundance

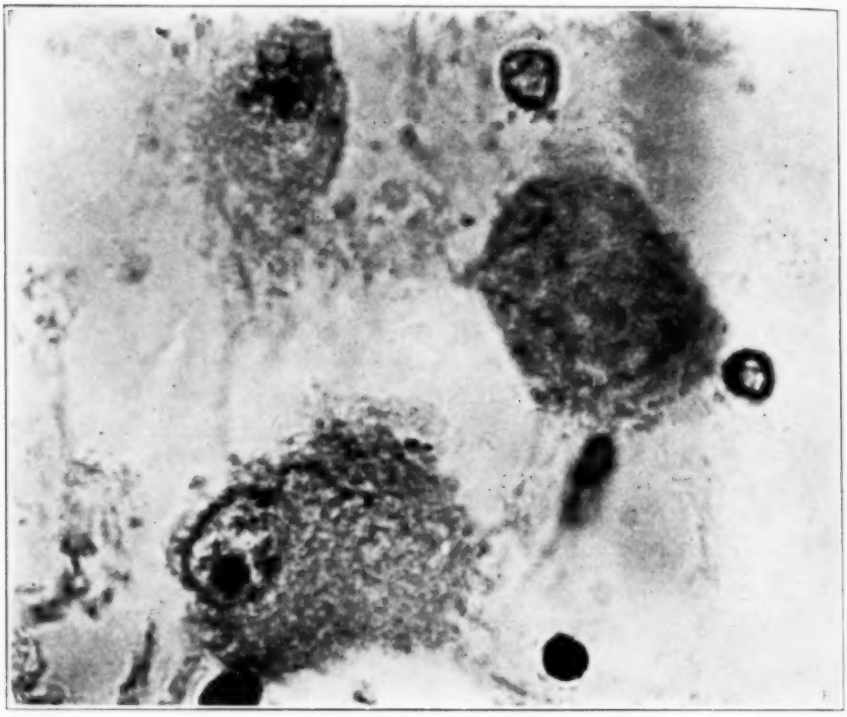


Fig. 12.—The absence of Nissl substance and the vacuolated appearance of the cytoplasm is clearly shown. In the cell to the right there is an indistinct sort of chromidial substance. Bielschowsky-Plein; × 1565.

of regressive forms suggest, however, that these formations are blastomatous and not merely congenital malformations. Many of the ganglion cells described in the reported cases of ganglioneuroma have been found to be multinucleated. Minot [21] stated that there is a multinuclear neuroblast stage in lower fishes. Kölliker (quoted by Beneke)

21. Minot, C. S.: Human Embryology, New York, The Macmillan Company, 1887.

stated that cells with two nuclei are found in younger animals in general, and Beneke [22] found that the celiac ganglion in fetuses and new-born infants contained many more ganglion cells with two nuclei than in the adult. These multinucleated cells have therefore an analogy in the development of ganglion cells in lower animals, and even in some sympathetic ganglia of adults. In their blastomatous development they tend to assume a form less mature than that seen in the adult nerve cell.

We believe that it is a misnomer to speak of the ganglion cells found in these tumors as neuroblasts. They are not neuroblasts. They differ from these cells in their size and general characteristics. They resemble neuroblasts only in the fact that some of them possess no poles, or a single or a double process. In our opinion these cells are better looked on as immature ganglion cells which have for some reason never gone on to total maturity. In our case they resembled ganglion cells, but had none of the inclusions of the bodies nor neurofibrils. In other instances these substances have been present in varying degree, and in one reported instance (Bielschowsky) the cells were practically mature ganglion cells. We think that we shall be more in harmony with the facts if we look on the cells in the ganglioneuromas as ganglion cells which have attained only partial maturity rather than as true neuroblasts.

22. Beneke, R.: Zwei Fälle von Ganglioneurom, Beitr. z. path. Anat. u. z. allg. Path. **30**:1, 1901.

CEREBRAL BIRTH PALSIES

A CONTRIBUTION TO THEIR PATHOLOGY WITH A REPORT OF A HITHERTO UNDESCRIBED FORM *

LEON FREEDOM, M.D.
BALTIMORE

The clinical symptomatology and pathologic anatomy of the cerebral birth palsies remain even today an open chapter in medicine. This is because there are many diseases that may give rise to the clinical picture of infantile palsy. Numerous investigators have attempted to classify all of the various causes; others claim these palsies to be due to hemorrhage or injury at the time of birth. Collier [1] considered them all due to a "primary degeneration of the cerebral pyramidal neurones." Investigations of the neuropathology of cerebral birth palsies, taken in the wider sense as described by Freud,[2] has convinced me that it is impossible to bring all of the various causes under one heading.

The confusion in the field was greatly increased by the work of Dr. Sarah McNutt [3] who, in 1885, described a case of "double infantile spastic hemiplegia" in a child born in difficult labor. A second case report followed, in which she generalized meningeal hemorrhage as the cause of all infantile spastic states that were dated from the time of birth and associated with difficult labor. Although it has been shown that Dr. McNutt misinterpreted her pathologic observations, and in spite of the numerous contributions to the literature on the cerebral infantile palsies, it is surprising how universally accepted her teachings have become.

The term "Little's disease" should be strictly confined to cases of cerebral diplegia associated with difficult labor; the term, however, has now become so broadened that, with but few exceptions, it is used synonomously with all cerebral motor disturbances present from the time of birth or shortly thereafter, irrespective of their association with difficult labor. Little,[4] in 1843, suggested that difficult labor might be an etiologic factor, but that lack of development of the cerebral tissues and meningeal inflammatory processes were the usual causes. A second

* Submitted for publication, Feb. 26, 1930.

* From the Department of Neuro-Pathology, University of Maryland.

1. Collier, J.: The Cerebral Birth Palsies, Brain **47**:1, 1924.

2. Freud, S.: Die infantile Cerebrallähmung, in Nothnagel: Spezielle Pathologie und Therapie, Vienna, 1897, vol. 9.

3. McNutt, Sarah J.: Am. J. Obst. & Gynec. **18**:73, 1885.

4. Little, W. J.: Tr. Obst. Soc. London **3**:293, 1862.

paper, in 1862, stated that nearly three quarters of all cases of spastic cerebral paralyses were caused by an intracranial hemorrhage at the time of birth. It was this work that Dr. McNutt corroborated.

As a fact, the cerebral infantile palsies are due to disturbances that are not uniform in etiology, clinical symptomatology, pathologic physiology or pathologic anatomy. Freud, in his classic monograph published in 1897, proved conclusively that the assumption of intracranial hemorrhage as the universal cause of infantile palsy was wrong. He demonstrated that not only was the clinical picture an extremely variable one, but that the etiology was equally so.

During the past fifteen or twenty years, there has arisen an enormous literature on the extrapyramidal motor disturbances; these have given much insight into the mechanism of these palsies.[5]

The following case is presented not only because of its unusual pathologic changes, but also to demonstrate the fallacy and incorrectness of assuming that all cases of cerebral infantile palsies are due to but one etiologic factor.

REPORT OF CASE

Clinical History.—A white woman, born in 1906, was brought to the hospital at the age of 19 because of her "mental condition." The following facts concerning the patient were elicited from the father: The mother was always a "bit nervous." In youth she had a "kind of St. Vitus Dance," the details of which he was unable to describe accurately. She was often "absent-minded" and on the very slightest causes became irritable and jumpy. Nothing definite concerning the early life of the mother could be elicited. She married in her early twenties, four years before the patient was born. She had two spontaneous abortions, both before the patient was born. Nothing is known of her immediate or remote family history. In 1906, four years after the marriage, the patient was born without difficulty or operative procedures. The following year a son was born; he was normal for his age mentally and physically.

During their married life, the mother was never "really sick." Her "nature" was healthy, only "there must have been something in her head which was not right." She was exceedingly nervous, irritable and jumpy; she had spells of despondency and occasional hysterical episodes. She died of acute lung infection in her late thirties. The father, aged 52, had had Potts' disease in his youth. He now had a marked dorsal kyphosis. His parents were living and healthy. He had two brothers and two sisters, all of whom were healthy and strong. He said that he had not had venereal disease, and except for the acute exanthems of

5. Jakob, Alfons: Die extrapyramidalen Erkrankungen, Monog. a. d. geb. d. Neurol. u. Psychiat., Berlin, 1923, vol. 37. Vogt, C., and Vogt, O.: Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:1919-1920, Ergnzungshft. 3, p. 627; Erkrankungen der Grosshirnrinde im Lichte der Topistik, Pathoklise und Pathoarchitektonik, Leipzig, J. A. Barth, 1922. Foerster, O.: Zur Analyse und Pathophysiologie der striären Bewegungestörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:1, 1921. Kleist, K.: Die psychomotorischen Störungen, Monatschr. f. Psychiat. u. Neurol. **53**:253, 1922.

childhood, had always been healthy. He was a lithographer. There was no history of mental or organic disease of the nervous system in his immediate or remote family.

During the pregnancy, the mother was nervous and irritable but not sick. She worked about the house, taking care of her household duties until the day before delivery. The child was born at full term, and no operative intervention was necessary. The child was not cyanotic, and nothing of importance was noted. On the day following delivery, both father and mother noticed that the child had a peculiar "turning and rolling movement of the eyes," the scalp was excoriated and the blebs on the scalp when punctured exuded an aqueous fluid. The child was never breast fed. The sores disappeared within several weeks on the application of an ointment prescribed by the family physician. For many months, however, the child had a "dandruff-like scaliness and roughening of the skin." The child was extremely dull and was unable to sit up until about the third year. At times she said words that sounded like "papa" and "mama." At the beginning of the fifth year she attempted to walk. Her gait was uncertain; she frequently fell, and on one occasion broke her forearm. At about this time the continuous rolling of the eyes ceased, and did not reappear until she had convulsive seizures, which commenced in the fifth year.

With the onset of a convulsive seizure, she would cry out and fall to the floor; she was unconscious; the eyes and mouth would turn to one side with twitching of one side of the mouth, followed by generalized convulsive movements. Such attacks would last about five minutes and were followed quickly by return of consciousness. Five minutes later she was again able to stand up and move about. At the beginning these seizures appeared about once or twice a month, later increasing to as many as ten or more daily.

She seemed to be "quite sensitive," could manifest happiness, and cried when spoken to in a gruff manner. She was able, however, to execute only the simplest of commands. Between the fifth and seventh year it was noted that "she kept her legs drawn up under her" and as she walked her legs were semiflexed at the knees. At the age of 8, this had developed into a permanent contracture. She was otherwise never ill; she never had any of the acute exanthems of childhood. She was unable to eat unassisted, nor could she take care of her physical necessities.

Between 9 and 10 there was a gradual onset of involuntary purposeless twitches of the muscles of the face, fingers and extremities. She was studied by a neurologist who presented her at a clinic of visiting physicians. She was given a series of intramuscular injections of sodium cacodylate, but without beneficial results.

During the years that followed she could perform only the most simple household duties, was never able to feed herself and had frequent epileptiform seizures, although there was slight improvement in physical appearance. At the age of 17, she was still unable to walk well and was practically bedridden. At times she was even unable to sit up in bed. At 18, because of her mother's death and since there was no one at home to take care of her, she was brought to the hospital.

Physical Examination.—At the time of admission she appeared considerably older than her years. She could neither stand nor walk. She gave her name unclearly, showed her tongue and held out her hand on request. The general bodily nutrition was moderately good. The skin of the entire lower part of the body, the hips, especially in the gluteal regions, thighs and feet showed a peculiar, rather dry hyperkeratosis with scaling. The forehead was low, the eyes deeply set, the expression idiotic. The ear lobes were long and not adherent. The dis-

tribution of hair on the body was normal. The pupils were equal and reacted well to light. The ocular fundus was normal. There was no nystagmus. The measurements of the body were: length of arms, 63 cm.; span of arms, 146 cm.; length from symphysis to right heel, 70 cm.; length from symphysis to left heel, 68 cm.; height of body, 153 cm., and circumference of skull, 51 cm.

The chest was normal; the abdomen showed no abnormality, and the pelvis and genitalia were normal.

Neurologic Examination.—The patient was unable to walk or stand; cooperation was not obtainable. She lay on her side, the forearms flexed on the arms and the arms closely held to the chest. The legs were flexed on the thighs, which were tightly flexed to the abdomen. Muscular development was fair in both upper extremities and not so good in the lower ones. At times the upper extremities were exceedingly rigid, a very striking clinical feature. Both wrists were hyperextended, and the thin, small fingers were frequently involved in athetoid movements. This was not noted in the toes. Sometimes she grimaced; there were occasional loud shrieks which lasted but a few seconds. At not infrequent intervals there was a twitching of the upper extremities and head. Often she extended the arms over her head as if reaching or groping for something. There was no muscular atrophy, paralysis or fibrillary twitching.

Deep reflexes: The biceps, triceps and periosteo-radial reflexes were lively and equal on the two sides. The patellar reflex was hyperactive; a definite patellar clonus was obtained on the right but was not sustained on the left. The achilles reflex was bilaterally hyperactive with sustained clonus. The superficial abdominal reflexes were not elicited. The Babinski sign was weakly positive on both sides; the Gordon, Oppenheim and Rossolimo reflexes were not obtained.

The cranial nerves were normal so far as could be determined. The blood and spinal fluid were normal.

Mental Examination.—The patient was completely demented; there was no spontaneous speech; when questioned she only mumbled an incoherent reply. She answered properly when asked to give her name. Her attention could not be held. The grimaces that she occasionally made were not associated with any emotion. She had to be fed, and was incontinent of bowel and bladder.

Course.—During her stay in the hospital for one half year after admission, the mental state remained the same; she had major diurnal and nocturnal epileptic seizures varying from one to twelve in twenty-four hours. She remained completely demented; at times she would hold out her hand when asked to do so; occasionally she smiled when addressed and made pitiful incoherent attempts at speech. There was no fever. The epileptiform seizures were not influenced by the administration of bromides or phenobarbital.

Six months after admission, she had a mild febrile attack of pyelitis which lasted several weeks. This was followed by a nonspecific diarrhea. The stools gave negative results on bacteriologic examination. The patient went rapidly down hill, and died of a terminal bronchopneumonia.

Clinical Diagnosis.—Little's disease with idiocy and epilepsy was diagnosed.

Autopsy.—Examination was performed twelve hours after death. There was bilateral bronchopneumonia. The thyroid gland was of normal consistency and size. The suprarenals were normal in weight and appearance.

Brain: The meninges were glistening in appearance, not thickened and not unusually adherent. The vessels were not deeply congested. The gyri presented no anomalies; the intervening sulci were slightly deeper and more pronounced than is usually the case, suggesting the possibility that the convolutions might perhaps be slightly diminished in size. The brain was cut into a number of

frontal sections, each about from 1.5 to 2 cm. in thickness. On fresh section no abnormality was noted in the cortex or subcortical white matter. The corpus striatum had a rather flecked and grayish-yellow mottled appearance which, in conjunction with the clinical picture, suggested the possibility of a status marmoratus of the striatum. The ventricles were normal.

The provisional anatomic diagnosis was: bilateral bronchopneumonia; status marmoratus of the striatum.

One half of the brain was placed in alcohol, the remainder in formaldehyde, except for a few small pieces of cortex and basal ganglia that were placed in

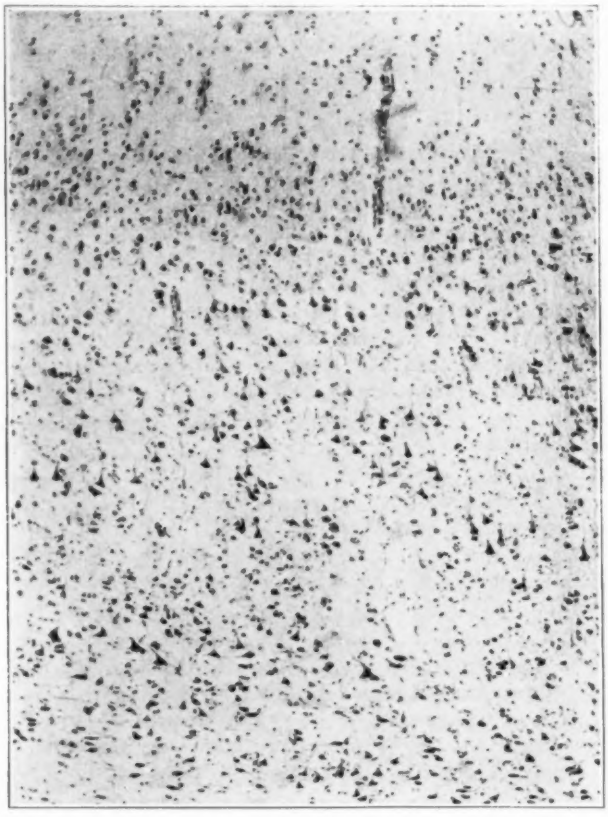


Fig. 1.—Area 9 of Brodmann. Note the focal and diffuse disappearance of ganglion cells without neuroglial reaction.

ammonium bromide solution for Cajal and Hortega stains; another frontal section through the basal ganglia was fixed in Müller's solution for a myelinated fiber stain.

Histology of the Brain.—In the granular frontal region (fields 10, 9, 45, 46, and 44 of Brodmann [6]) relatively few changes were found in the cortex. The cyto-architecture was well preserved, though there were areas in which there

6. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde, Leipzig, Johann Ambrosius Barth, 1909.

had been a focal falling out of cells (Verödungsherde), especially in the third Brodmann layer (fig. 1). The ganglion cells were well preserved, and over the greater portion of the frontal lobe there was very little evidence of cortical destruction. Figure 1 is typical of the type of involvement in the posterior lateral portion of the granular frontal region. The cells had been rather diffusely destroyed, and the foci of cellular falling out were more marked in laminae 3 and 5. There was no neuroglial reaction. Here and there small neuronophagocytic accumulations of glia were noted at the site of a broken-down ganglion cell (fig. 2). Where the foci in which the cells had disappeared were most numerous, the surrounding ganglion cells were also degenerating.

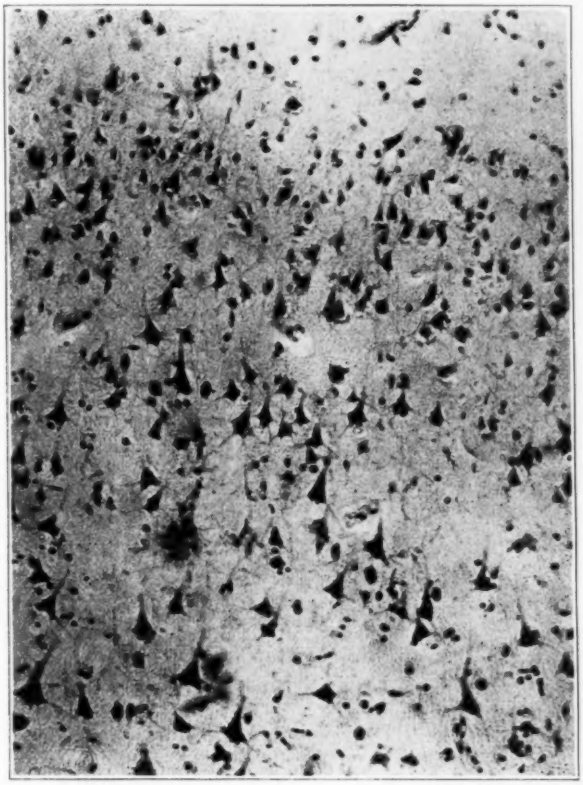


Fig. 2.—Same area as in figure 1, showing the neuroglial rosette.

In such ganglion cells, the Nissl bodies were clumped into deeply staining homogeneous masses in which the nucleus was no longer discernible. Other ganglion cells stained palely and seemed to fade out gradually into the surrounding intercellular substance. Figure 2 demonstrates a typical area in the posterior granular frontal region in which the entire cortex contained cells in various degrees of degeneration within the foci as described and an occasional neuroglial rosette.

The meninges over the entire frontal region were normal with the exception of the rolandic region and the extended motor cortex. The neuroglia cells, too,

showed degenerative changes, but as a whole were relatively little involved. There was a slight hyperchromatosis of the nuclei of the Cajal and oligodendroglia cells, and there were progressive changes in the microglia, especially in the neuroglia rosettes. The cortical capillaries were not increased. Where the cortical changes were most pronounced the endothelial cells showed slight hyperchromatosis, were somewhat shrunken, and contained a slight amount of fat in the cytoplasm. The adventitial cells were also more deeply stained than normal, at times even pyknotic. In many instances the cytoplasm contained a greenish-yellow pigment.

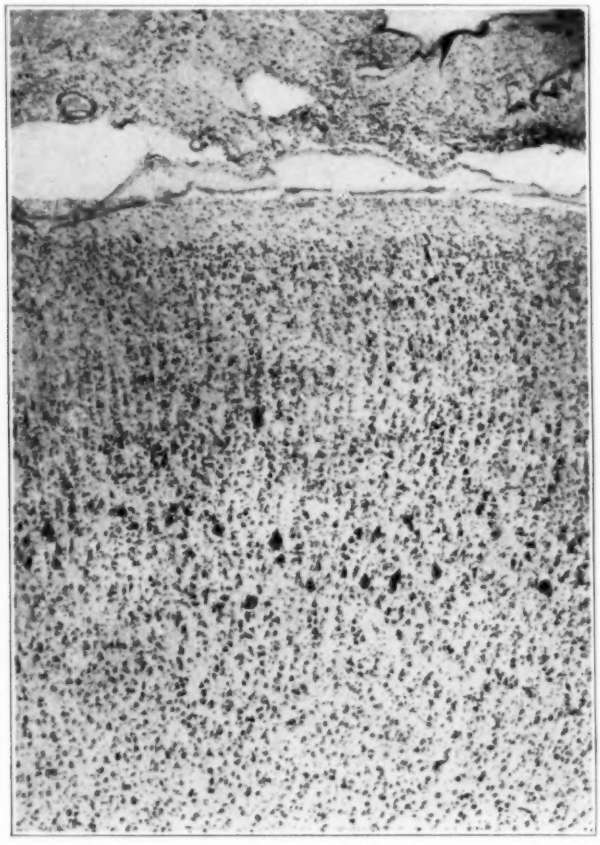


Fig. 3.—Rolandic region, showing chronic leptomeningitis, proliferation of the neuroglia in the molecular layer and rarefaction of the cells in the pyramidal layer.

The rolandic region showed changes of a more marked degree. The uppermost portion of the cortex was more severely involved than the lower. Numerous cells had disappeared from the second and third laminae. The foci had become confluent, forming large patches in which very few cells were found. The neuroglia cells, especially the macroglia and the oligodendroglia, were somewhat increased; the former were fairly numerous in the uppermost portion of the cortex. In figure 3, with a magnification of 45, the proliferated glia cells are to be seen in the zonal layer. The alteration of the giant cells of Betz was very striking. All the Betz cells were swollen. The contrast in their size to the smaller elements

that surrounded them made them strikingly prominent. Even the processes might be followed for some distance from the cell body, a feature not unusual in blue preparations. The tigroid bodies in the center of the cell had been transformed into a dustlike substance, and the nucleus had been pushed to the side, as though forced into this eccentric position by the increase in intracellular pressure. The nucleus might even be extruded from the cell body (fig. 4). A few Betz cells were so markedly degenerated that merely shadows of the former cell body remained. Transition to this shadow form might be noted throughout the entire rolandic cortex. In spite of the marked proliferation of the satellite and surrounding glia, no neurophagocytic glia rosettes were found. Many of the larger pyramidal cells in the middle and deeper cortex were also involved in various degrees of deterioration.

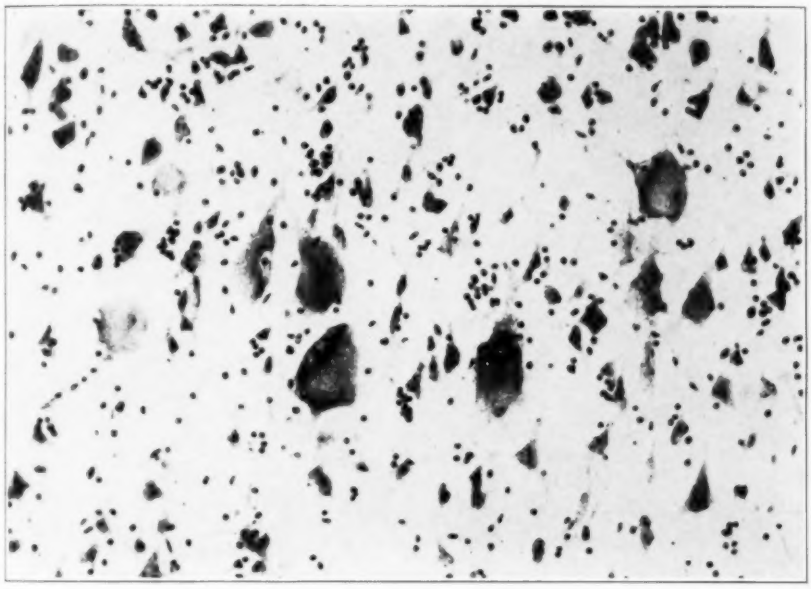


Fig. 4.—Swelling and eccentric position of the nucleus in the giant cells of Betz, with an extreme degree of chromatolysis.

The leptomeninges over the rolandic region, on the lateral surface as well as over the paracentral lobule, were markedly thickened. This was due to hyperplasia of the connective tissue. In places there were accumulations of lymphocytes and an occasional plasma cell. The smaller vessels of the pia were deeply engorged; in some places the blood had extravasated into the surrounding tissues, but not into the cortex.

The phenomena described were also to be found in the Broca field. The retrocentral convolution (fig. 5) was much more seriously involved. The transition between the motor cortex and the decidedly granular retrocentral cortex was striking in the severity of the degenerative changes. The entire breadth of the cortex showed diffuse falling out of cells, in places focal, in others widespread, with a relative exemption, however, of the second and fourth layers of Brodmann. These, too, suffered a loss of cells, though their continuity was not interrupted. The ganglion cells were all more or less degenerated. Those in the granular layer

suffered relatively less. The neuroglia, particularly the fiber-forming astrocytes, were markedly proliferated, forming beneath the meninges a rather dense sheath visible in Nissl preparation as a homogeneous, translucent, acellular, thickened membrana limitans gliae. The capillaries increased, incidentally to the shrinkage of the tissues (Cerletti). The cells of the capillary walls showed regressive changes. In lamina 5 some of the larger pyramidal cells were relatively intact.

The subcortical white substance of the retrocentral areas contained numerous proliferated glia that showed all the stages from slightly hypertrophied rod cells

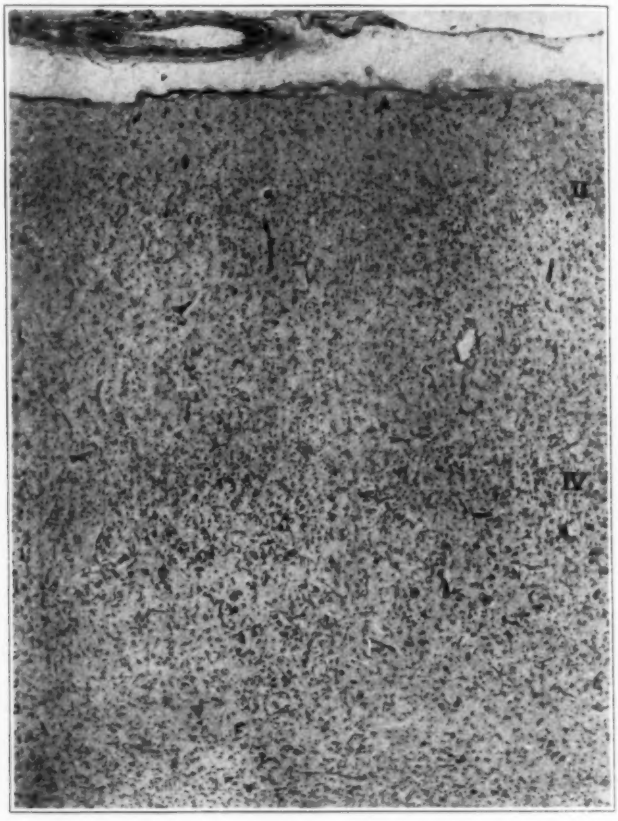


Fig. 5.—Disappearance of practically all cells with the exception of laminae II and IV, which are relatively less involved. The cells are mostly neuroglial.

to the formation of fully developed myelophages and "Körnchen" (neuroglial phagocytic) cells. These cells conformed with those described by A. Jakob and his school (A. H. Schroeder [7]) in their studies on secondary degeneration.[8] The

7. Schroeder, A. H.: Normale und pathologische Anatomie und Histologie des Grosshirns, Vienna, Franz Deuticke, 1929.

8. Jakob, A.: Ueber die feinere Histologie der sekundären Faserdegeneration in der weissen Substanz des Rückenmarks, in Nissl: Histologische und histopathologische Arbeiten über der Grosshirnrinde, Jena, 1913, vol. 5.

larger ganglion or giant cells, which are found normally in the retrocentral cortex close to the motor area, also showed the changes described.

This laminary degeneration in various stages of activity was to be found throughout the entire partietal, occipital and temporal cortex. The degree and severity of involvement, however, was not uniform. Immediately adjacent to an area of almost completely disintegrated cortex might be found a relatively free surface. The part of the brain posterior to the fissure of Rolando was, neverthe-

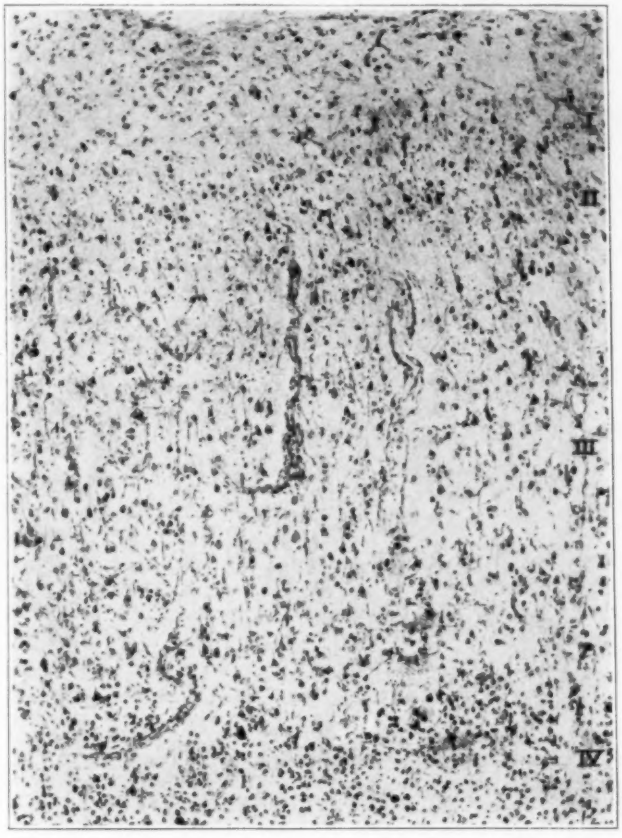


Fig. 6.—The granular insula. Note the striated appearance due to the proliferation and hypertrophy of the microglia; very few ganglion cells remain.

less, the site of much more marked destructive changes than the frontal lobe (fig. 6). The posterior or granular portion of the insular cortex showed the process in the height of activity. Large numbers of nerve cells had been destroyed; many were in various degrees of destruction. Although the most marked changes occurred in the third and fifth layers, the activity was by no means limited to them. In places the cortex had a finely striated appearance, caused by the enormous proliferation of the Hortega glia cells which, with their hypertrophied bipolar processes, gave rise to this unusual picture.

The changes in these microglia cells was very similar to those described by del Rio Hortega [9] and Ramón y Cajal [10] and simulated the picture found in paralytica dementia as reported by the latter. In figure 7, with a higher magnification, the elongated microglia can be readily seen. In the center of this figure is shown a smaller cortical vessel with numerous, newly formed capillary buds. The endothelium and adventitial cells were all greatly enlarged, increased in number and in places so similar that it was impossible to differentiate them. Endarteritis of the smaller cortical vessels was noted in all sites of severe active cortical destruction in which there was an accompanying neuroglial proliferation. Here and there a slight perivascular infiltration of small round cells might be found, but this was not constant even in areas so severely involved as this. Scattered among these microglia cells were a few greatly hypertrophied macroglia, the so-called "gemästete" forms described by the Germans.

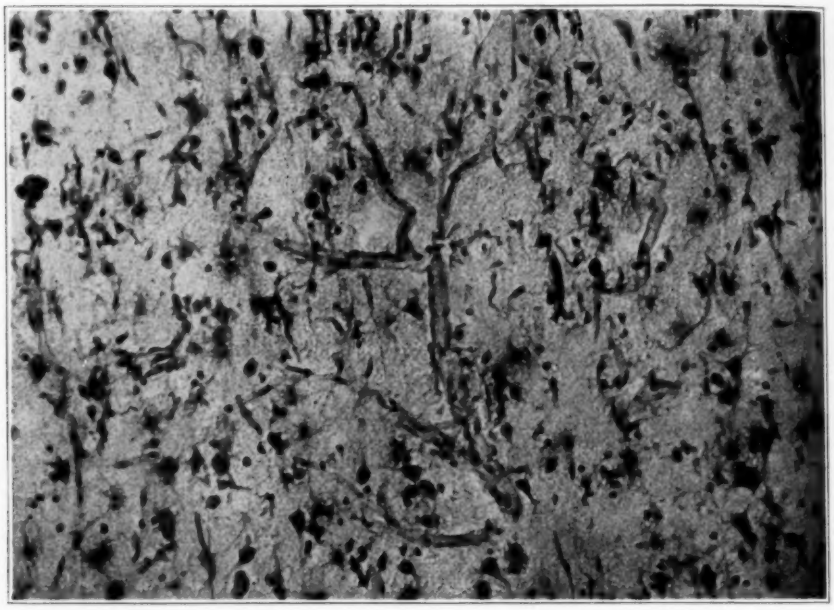


Fig. 7.—Higher magnification of figure 6. It shows elongated microglia, the moderate capillary proliferation and endarteritis and the blurred homogeneous cytoplasm of the proliferated macroglia.

The anterior portion of the insula was comparable in the nature of its pathologic changes with the frontal lobe. The transition between the agranular anterior insula, which was relatively slightly involved, with that of the severely degenerated granular insula posterior to the central sulcus was striking.

---

9. del Rio Hortega: El "Tercer Elemento" de los centros nervos, Bol. de la soc. españ. de biol. **9**:68, 1919.

10. Ramón y Cajal, S.: Contribution à la connaissance de la neuroglia cérébrale et cérébelleuse dans la paralysie générale progressive, Trav. d. lab. de invest. biol. Univ. de Madrid, 1925, p. 241.

Sudan III (fig. 8) and scarlet red fat preparations showed the presence of large amounts of lipoids stored in the cytoplasm of the Hortega microglia; there was practically none in the surrounding degenerated bodies of the nerve cells or in the macroglia.

The cortex of the visual and visuopsychic regions (fields 17, 18 and 19 of Brodmann) also showed severe degenerative changes. Here, too, they were focal in character, though the tendency to predilection for the third and fifth layers was noted. In some places the cortex, except for a mild diffuse "falling out" of cells in which the architectural structure had not been destroyed, otherwise showed nothing unusual (fig. 9). In other places practically the entire cortex (with the exception of the granular layers, particularly the fourth) had been destroyed. Figure 10 shows the transition between the calcarine and the occipital cortex. The splitting of the granular layer can be recognized readily. The great number of cells in this picture are proliferated glia, most of the nerve cells having been destroyed (fig. 11). The neuroglial reaction here, however, is quite different from that noted in the posterior insular cortex. The neuroglia cells were mostly large, "stuffed," enormously hypertrophied macroglia cells. Great clumps of homogeneous cytoplasm, which contained from one to three or even four large nuclei, replaced the destroyed nerve structures. These macroglia cells were protoplasmatic forms which had become fiber-forming. Many of the protoplasmatic astrocytes with specific stains showed beginning formation of neuroglia fibers in their cytoplasmic processes. These macroglia clumps were the so-called "Gliarasen" of the German school. A few hypertrophied bipolar microglia cells were scattered among them.

The smaller cortical vessels and capillaries showed marked endarterial changes. An occasional small lymphocyte might be found between the proliferating vessel wall cells (fig. 11).

The temporal cortex showed two distinct types of pathologic phenomena. The entorhinal region of Rose,[11] especially the anterior region of the uncus, showed changes very similar to those noted in the calcarine cortex. The cornu ammonis, particularly the h4 and h5 fields of Rose and Vogt, showed diffuse "falling out" of cells. There was no neuroglia reaction. The subiculum and presubiculum were severely damaged. Figures 12 and 13 demonstrated the severity of the process in the entorhinal cortex. Nothing remained except a few cells in the outer cortical layers. The neuroglia were mostly fiber-forming astrocytes with large succulent bodies. In toluidine blue preparations, the cytoplasm resembled milk glass. A few contained moderate amounts of a greenish-yellow refractile pigment. The subcortical white substance here also was rich in neuroglia.

The remainder of the temporal isocortex showed widespread destructive changes. The laminary degeneration extended over successive gyri, and was not limited to any one cyto-architectural area. The third and fifth layers had suffered most. Figure 14 shows a small gyrus in the middle part of the first temporal convolution in which the third layer is practically desolate.

Beneath the pia there was a fairly broad refractile band in preparations stained with toluidine blue. This contained relatively few cells. The third layer of the temporal cortex, in contrast to the remainder of the cortical gray matter, contained relatively few cells. The middle portion of the third layer of the cortex in places

11. Rose, M.: Der Allocortex bei Tier und Menschen, J. f. Psychol. u. Neurol., **34**:1, 1926.

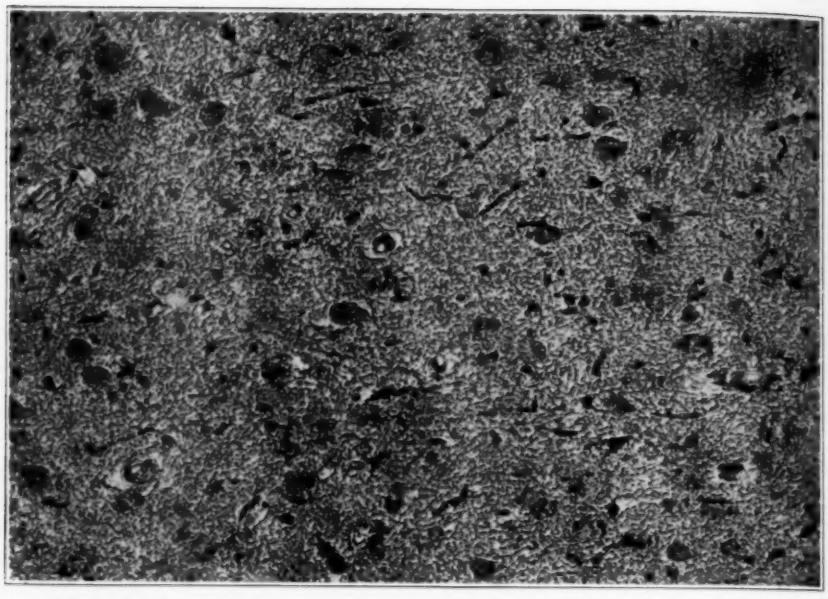


Fig. 8.—Darkly staining fat particles in the cytoplasm of the elongated Hortega cells. Sudan III stain.

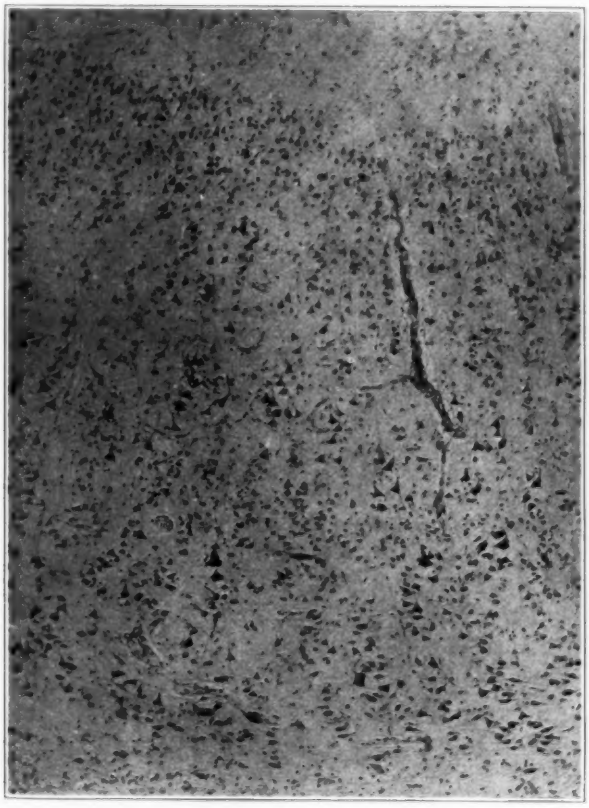


Fig. 9.—Area 18; the visuopsychic area of Campbell. Rarefication of the ganglion cells without distortion of the cyto-architecture of neuroglial replacement.

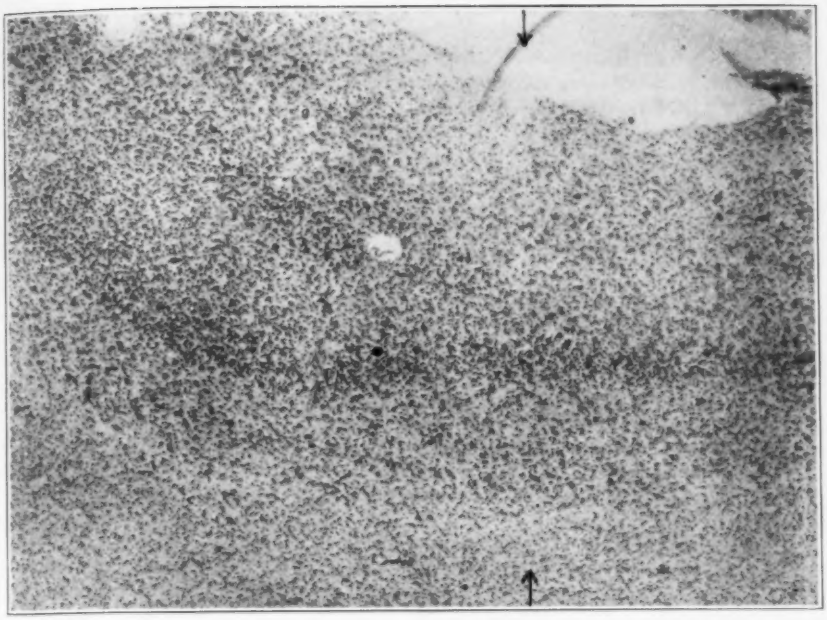


Fig. 10.—The area to the right of the arrows is area 18; to the left, area 17. Note the "*Y*" shape of the splitting of the internal granular layer of area 18 into the *IV'a*, *IV'b* and *IV'c* of the area striata, Brodmann. Only this granular layer remains; the remainder of the pyramidal cells have disappeared.

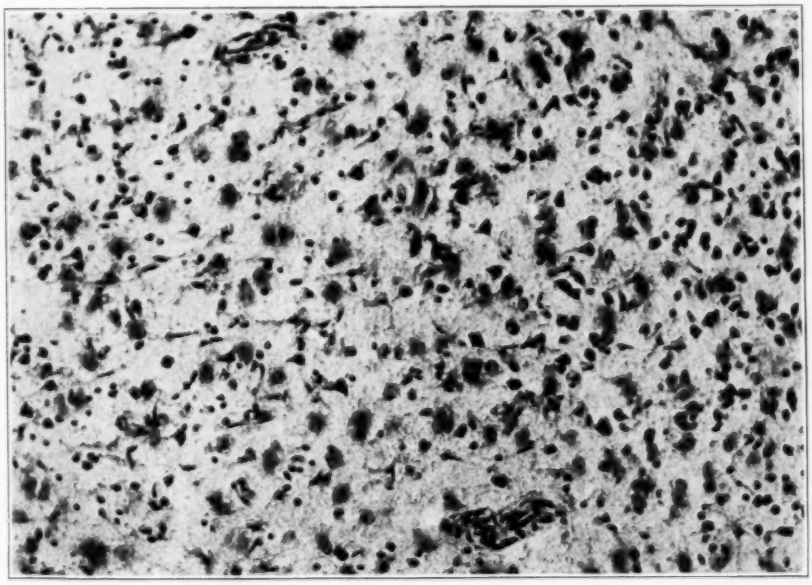


Fig. 11.—The calcarine cortex. Marked proliferation of the Cajal macroglia. Compare this neuroglial reaction with the type in figures 6 and 7.

had a peculiar, honeycombed, spongy appearance. The victoria blue neuroglia fiber preparations showed the dense meshwork of fibers replacing the destroyed cortex. In the preparation, the dense thickened membrana glia beneath the leptomeninges was seen as a deeply stained dark blue stripe. Normally the middle portion of the cortex contains far less neuroglia fibers than are seen in figure 15. The spongy appearance corresponded to the so-called "status spongiosus" of Fischer,[12] Jakob[13] and Spielmeyer.[14] Around some of the dilated cortical vessels was a thickened membrana perivascularis gliae.

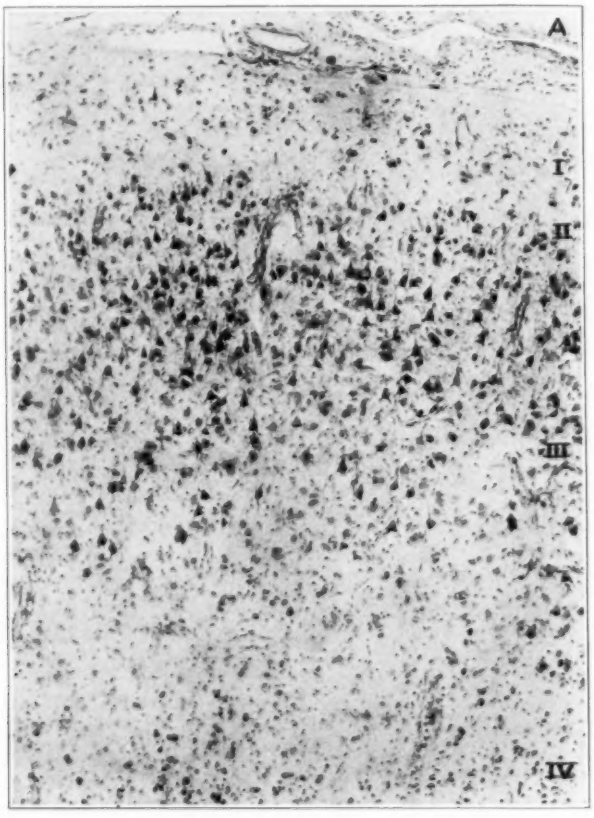


Fig. 12.—The temporal lobe, in which the process is at the height of its activity. The involvement of the ganglion cells seems to start in the deeper cortex and ascend into the upper. *A* indicates the meninges. *I* represents the first lamina; *II*, the second; *III*, the third, and *IV*, the fourth.

12. Fischer, O.: Der spongiose Rinderschwund, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:1, 1911.

13. Jakob, A.: Paradoxale Kinderlähmung, Deutsche Ztschr. f. Nervenh. **68-69**:313, 1921.

14. Spielmeyer, W.: Die histopathologie Zusammengehörigkeit der Wilsonschen Krankheit und der Pseudosklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:312, 1920.

The striatum, both caudatum and putamen, had suffered severely. Here the small striatal cells were more involved than the large elements. In many places there had been a focal falling out of cells involving both elements. Most of the cells showed more or less marked degeneration, though there are places in which the striatum was perfectly normal. There was no decided increase in "pseudocalcium," nor was the striatal pigment unusually increased (Spatz [15]).

In both the external and internal portions the pallidum was even more seriously involved than the striatum. There were large areas in which practically

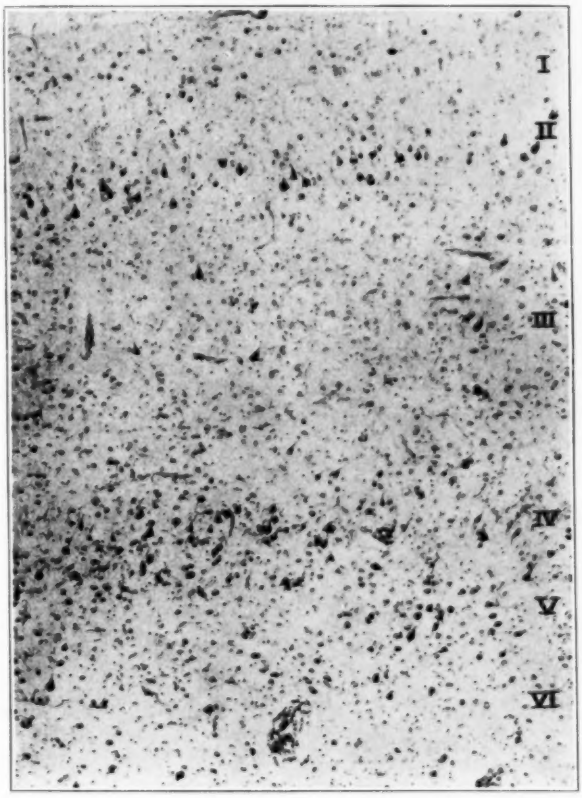


Fig. 13.—The temporal lobe, showing the result of the "attack." Some semblance of lamination is present in *II* and *IV*; the pale, faintly stained cells are neuroglia cells, the larger, darker staining elements are the surviving ganglion cells.

not a single pallidal cell remained. The few that did persist, however, were relatively intact. There was a marked reactive neuroglial proliferation (fig. 16).

The various thalamic nuclei were all more or less involved. In the ventral nucleus there were numerous neurophagocytic cells and small glial rosettes (fig. 17). Here the neuroglial reaction was chiefly protoplasmatic. Other thalamic

15. Spatz, H.: Ueber Stoffwechseleigentümlichkeiten in der Stamganglien, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:641, 1922.

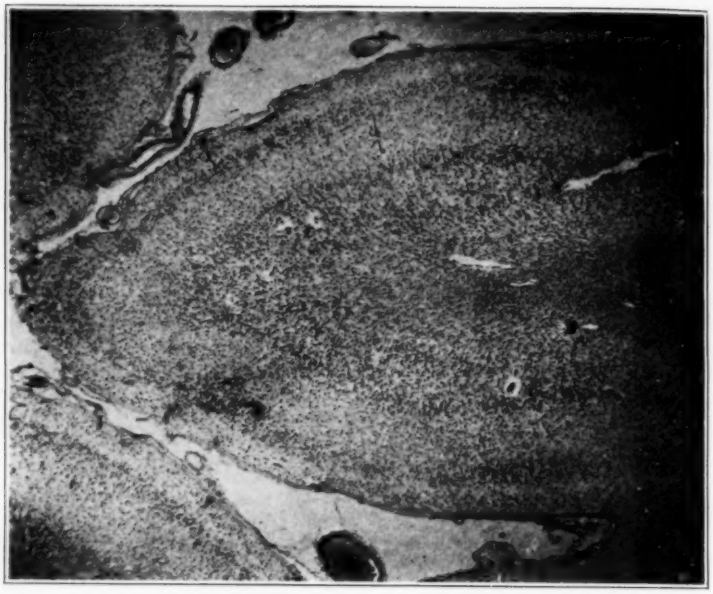


Fig. 14.—The temporal lobe, Heschl's gyrus, showing distinct laminary degeneration of the third cortical layer.

Fig. 15.—At *A* there is a markedly thickened membrana beneath the meninges. Note the thickened wall of glial fibers around the blood vessels. "Victoria blue" neuroglia fiber preparation.

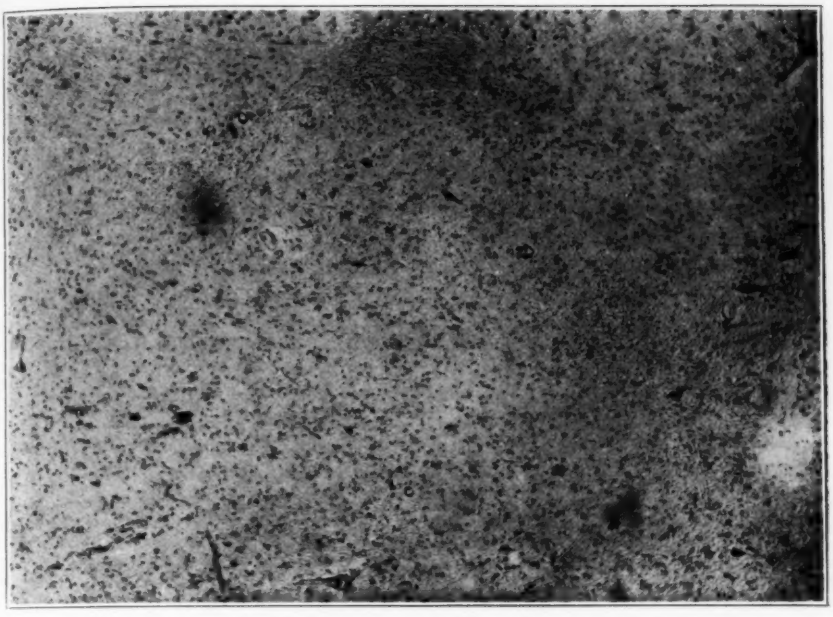


Fig. 16.—The pallidum, showing very few remaining pallidal cells.

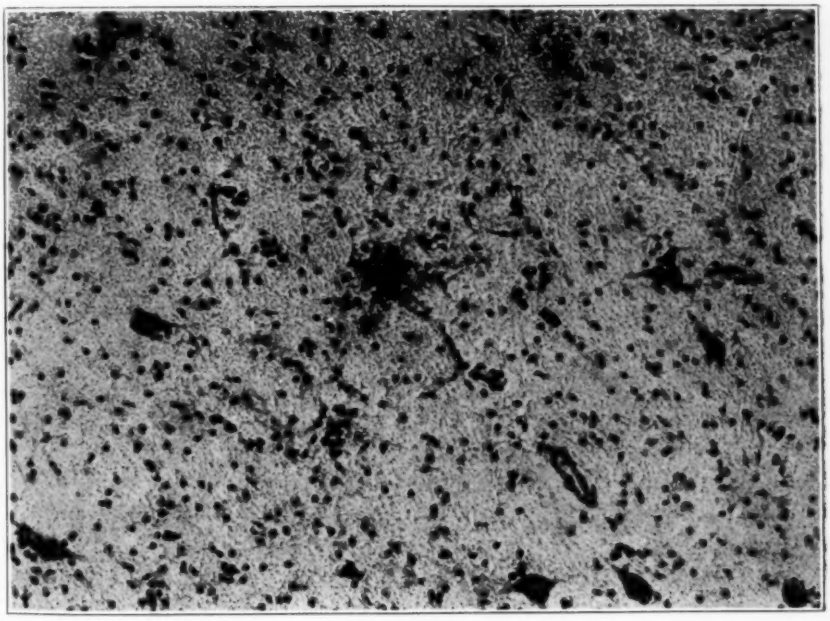


Fig. 17.—The thalamus, showing a glial rosette and a paucity of ganglion cells.

nuclei had suffered a great loss of cells, but without a reactive glial proliferation. In some places both nerve cells and glia had totally disappeared.

The hypothalamus was most markedly involved. Nearly all of the hypothalamic nuclei were being attacked, and there was no evidence of older activity or scar.

The cerebellum was surprisingly free. An occasional Purkinje cell showed chronic degenerative changes. The dentatum, on the other hand, had lost many of its elements. The lipophilic cells of the dentate nucleus showed even greater fat content; many cells presented chromatolysis and vacuolization indicative of cellular degeneration. From the pathologic picture it was noted that the process was purely degenerative. Scattered throughout the subcortical white substance, and also here and there throughout the gray cortex, were moderately infiltrated small blood vessels. The infiltration was composed of small lymphocytes, no plasma cells, an occasional polyblast and sometimes a macrophage, its cytoplasm filled with a greenish-yellow pigment. There was no relationship between the constancy of these infiltrated vessels and the severity of the destructive process in the cortex. It is for this reason that I considered this phenomena a "symptomatic inflammation" in the sense of Lubarsch.[16] Such pictures are not infrequent in pure degenerative processes of the central nervous system.

Comment.—The cortical changes were most marked in those parts of the brain posterior to the fissure of Rolando. The frontal lobe in its entirety was nowhere as severely involved. The changes in the temporal lobe seemed to be the oldest, for here the process had come to its termination, and a scar in the nature of a diffuse neuroglia fiber proliferation with status spongiosus was all that remained of the former gray substance.

The process in the occipital and parietal cortex was focal in distribution. There was no predilection for any one particular cortical field nor, with the exception of the third layer, for any one lamina. The process might extend over several continuous convolutions without regard for the boundaries of any field. With the enormous proliferation and overwhelming majority of the fiber-forming astrocytes, the relatively fewer microglia fibers, the process was considered to be not as old as that in the temporal brain.

The retrocentral gyrus had suffered severely. The entire posterior wall of the central sulcus, including the cap of the retrocentral convolution, possessed only the two granular layers, and even these in places had lost many of their cells. The gyrus as a whole was slightly shrunken, and the numerous blood vessels were due only to the relative increase incident to shrinkage of brain substance.[17] The portion of the insula posterior to the central sulcus showed the process in the height of its activity. Ganglion cells were being rapidly destroyed, and the

16. Lubarsch: Entzündung, in Aschoff, L.: Pathologische Anatomie, Leipzig, Johann Ambrosius Barth, 1921.

17. Cerletti: Die Gefässvermehrung in Zentralnervensystem, in Nissl: Histologische und histopathologische Arbeiten über der Grosshirnrinde, 1910, vol. 4.

mighty proliferation of elongated bipolar microglia cells gave the cortex a finely striated appearance. All of the various phases of the changes from bipolar microglia to rounded out "Körnchenzellen," mononuclear large phagocytes of neuroglial origin, may be seen. In places the entire background had a granular, somewhat dull, grayish, broken-down appearance, suggesting that here the process had gone on nearly to complete softening. It corroborated well the fact brought out by Spielmeyer [14] in his work on the histologic relationship of Wilson's disease to the Westphal-Strümpell pseudosclerosis group, except that the changes that he described in the striatum in this case applied to the cortex.

The absence of reactive neuroglial proliferation in the frontal cortex was striking. In spite of the focal and diffuse disappearance of nerve cells there had been very little glial increase. The neuro-nonphagocytic glial rosette found throughout the frontal cortex was only occasional. It seems that the process started in a focal falling out of cells with subsequent glial rosettes, as has been described in the frontal lobe.

The striatum had lost many of its elements, especially the small striatal cells, though the large ones had by no means been exempt. There had been a diffuse Cajal glial proliferation, but the process had nowhere gone on to scar formation.

The pallidum had been even more severely involved than the striatum. There were large areas in which not a single pallidal cell remained. Those that remained showed a varying degree of degenerative changes, more marked in comparison with those seen in the remaining striatal cells.

The hypothalamus was so markedly involved that is was impossible to recognize any of its nuclei. In the hypothalamus, as well as throughout the entire thalamus, numerous neurophagocytic figures were found. This suggested the probability of more recent and active destruction of the cells.

The substantia nigra and corpus luysii were relatively free from loss of cells. The nucleus ruber was mildly involved.

The cerebellar cortex of the hemispheres, vermis and flocculi was relatively free. The Purkinje cells had been touched but little. In places the Bergman's glia were moderately increased. There was an occasional Fañanas cell in the molecular layer; the microglia were unchanged. Silver nitrate preparations (Cajal method) showed no obvious changes in the climbing or mossy fibers. The dentatum, on the other hand, had been seriously involved. There was a decided diffuse loss in cells; those which remained were more or less seriously degenerated, and the lipophilic cells of this nucleus had all undergone still more marked fatty degenerative changes.

The nuclei of the lower brain stem and cord were free. The pyramidal tracts were in the main intact, and only an occasional fiber showed pathologic changes.

In résumé, this process started with changes as noted in the frontal cortex; the activity increased, as shown by the marked microglial proliferation in the posterior insula. A still further progression was noted in the parietal and occipital cortex, where the macroglia cells were already undergoing fiber-forming changes. The end of this process was found in the temporal part of the brain. Here, a scar terminated the cortical destruction. The parts affected, in the order of severity, were (1) cortex, (2) basal ganglia and (3) dentatum.

Thyroid Gland.—This gland, which was normal in gross appearance, presented an extremely unusual microscopic condition. The colloid content was diminished in amount; there was considerable increase of the interacinal connective tissue and a rather marked diffuse infiltration throughout the entire gland substance, small round cell in type. The thyroid gland was the only one of the endocrine system to show any changes. On low magnification the extreme richness in small round cells throughout the entire glandular substance was noticeable. The walls around the acini were greatly thickened, and the colloid content was materially diminished. There were no obvious changes in the epithelial cells of the acini.

COMMENT

From the variations in the pathologic pictures it can readily be noted that one was dealing with different chronologic stages of a diffuse process. This process was at the height of its activity in certain portions of the brain, as in the temporal gyri and parts of the rhinencephalon the process was no longer active, but had gone on to scar formation. It seems, then, as though the earliest changes of this process are manifested by degenerative phenomena with subsequent focal disappearance of the ganglion cells, with or without neuronophagocytosis. The changes in the temporal portion of the brain without doubt were the oldest, the scar of the process. The end-product of this process was scarring, not as usually meant, however, but in the production of a fairly dense mass of neuroglia fibers in places ordinarily not the site of many fibers. This applies especially to the third layer, in which the normal amount of neuroglia fibers was particularly scanty (Weigert, A. H. Schroeder and Freedom). The background of the cortex, as seen in Nissl preparations, had a peculiar loculated appearance, to which O. Fischer gave the name "spongiöse Rindenschwund," and later Spielmeyer the name "status spongiosus."

Spielmeyer rightly emphasized the presence of status spongiosus as a scar formation representing the end-product of a process, but caused by the local peculiarities of the tissue in the presence of a rapid and massive destruction of tissue. Jakob [18] added a third factor, the type

18. Jakob, Cristfried: Das Menschenhirn, Munich, 1911.

of connective tissue reaction. In places in which the glia cells did not suffice to form a heavy scar, a paucity in glia fibers was noted, and the tissue took on this spongy appearance. When the substance defect is represented by a terminal, tightly knitted ample scar of neuroglia fibers, connective tissue or both, this condition is known as status impletus, gliosus or gliofibrosus.

The end-product of this process may therefore be spoken of as status impletus gliosus. Even though there were places in which the proliferation of capillaries in the cortex was marked, no connective issue fibers made up any part of this scar.

There was, however, an increase in vascularity of the temporal cortex, but comparison with the normal leads me to believe that this was a relatively vascular increase (Cerletti) incident to shrinkage and atrophy of the tissues. The insular cortex was also highly interesting in the nature of its pathologic changes. Here the process, according to the criteria of degeneration phenomena, was at the height of its activity. The microglia cells showed all the transition forms from those slightly progressively changed to fully developed "Körnchenzellen" (neuroglia phagocyte) forms; their cytoplasm was filled with degeneration products; the groundwork of the cortex had a dull grayish color and in places an amorphous granular appearance.

It was in a stage close to an actual softening, such as occurs incident to vascular occlusion. A striking proliferation of newly formed capillary shoots was found throughout. I am convinced, therefore, that there is but a slight degree of difference between degeneration and actual softening. This holds true for the cortex as it does in the basal ganglia, a fact demonstrated by Spielmeyer.[14]

What, then, is the nature and etiology of this diffuse, destructive, degenerative process which, judging from the clinical history, had been present from the earliest days of extra-uterine existence?

One notes that the process involved the cortex, basal ganglia and dentatum. The question naturally arises as to the possibility of a "system" involvement. Phylogenetically older and recent portions of the cortex were equally severely included in the process. The striatum and lowermost cortical layers in the sense of Christfried Jakob[18] were certainly not as markedly diseased as the uppermost cortical layers. So far as can be determined, there is no association between the severity of the changes in the cortex and those in the thalamus as indicated by Nissl.[19] The changes in the pulvinar were certainly not as marked, nor could they be brought into correlation with the focal areas of destruction in the angular and supramarginal gyri. There was no relationship in the pathologic changes in the neocerebellar or paleocere-

19. Nissl, F.: Die Grosshirnanteile des Kaninchens, Arch. f. Psychiat., vol. 52, part 3.

bellar parts of the cerebellum, dentatum or inferior olive (Bolk,[20] Ingvar [21] and Winkler [22]).

Nevertheless, this process involved in the order of severity, cortex, striatum pallidum and nucleus dentatus. Numerous cases have been reported in the literature of the past several decades in which severe degenerative phenomena have been found in the portions of the brain mentioned. The work of C. and O. Vogt, A. Jakob, F. H. Lewy and O. Foerster, as well as numerous isolated case reports of diseases of the extrapyramidal system, have shown the frequency with which degenerative phenomena have been found. No case has been found, however, in which the pathologic picture closely approximated the one in the case herewith presented.

In C. Vogt's original description, she does not mention changes in the cortex or dentatum. Scholz [23] and especially Onari,[24] working in A. Jakob's laboratory, reported cases in which not only was the striatum the site of severe degenerative changes, but the cortex was equally severely involved. In Onari's case the dentatum was also diseased. In the classic case of Vogt there was a neuroglial reaction, whereas in the case of Scholz a marked glial proliferation was found. Onari's case in this respect was atypical. The chief localization of the pathologic changes was in the striatum, whereas the pallidum, cortex and remaining portions of the brain suffered in a much lesser degree. Onari described a case of status marmoratus of the striatum combined with status dysmelinisatus of the pallidum. In this case, too, there was moderately severe cortical degeneration; the basal ganglion changes, however, ruled the pathologic picture.

What at first appeared to be a status marmoratus of the striatum in the fresh section was not corroborated by Weigert preparations. The nature of the cortical process was also different from that described by Onari. In my case the cortical changes were much more diffuse and prominent.

Filimonoff [25] reported the case of a child aged 8 months, born of a mother who had suffered a severe psychic trauma during pregnancy.

20. Bolk, L.: Das Cerebellum des Säugetiere, Jena, Gustav Fischer, 1906.

21. Ingvar, Sven: Zur Phylo- und Ontogenese des Kleinhirns, Folia neurobiol. **11**:205, 1919.

22. Winkler, C.: Manuel de neurologie, Haarlem, de Erven F. Bohn, 1927, vol. 1, pt. 3.

23. Scholz, W.: Klinische, pathologisch-anatomische und erbbiologische Untersuchung bei familiärer diffuser Hirnsklerose im Kindesalter, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:651, 1925.

24. Onari, K.: Ueber zwei klinisch und anatomisch kompliziert liegende Fälle von Status marmoratus, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:457, 1925.

25. Filimonoff, J. N.: Charakteristik der doppelseitigen Athetose des Kindesalters, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:197, 1922.

In addition to slow psychic development, she started to walk at 5 years of age. A bilateral progressive athetosis ruled the clinical picture. He reported severe destructive changes in the striatum and pallidum, which he considered to be hypoplastic and atrophic. These were combined with injury to the outer layer of the centralis anterior, but he did not give details of other cortical changes.

A case was described by Hallervorden and Spatz [26] in which there was, clinically, a progressive, generalized stiffening. A living sister of the patient had chorco-athetoid movements. In this case there were, in addition to the severe cortical ganglion cell degeneration and pallidum changes, severe destructive phenomena in the zona reticulata of the substantia nigra.

Another group of cases is now known collectively as the Wilson-Westphal-Strümpell pseudosclerosis disease (Spielmeyer [14]). In these cases the basal ganglia changes predominate over those of the cortex and dentatum. Though not necessarily, these may be combined with cirrhotic changes in the liver. Striking and exceedingly characteristic of this group is the presence of the large, so-called atypical glia cells of Alzheimer. The absence of these cells and of the Fleischer corneal ring of greenish pigmentation excludes my case from the pseudosclerosis group.

The cases described by Jakob [27] and Creutzfeld,[28] now known as the Jakob-Creutzfeld spastic pseudosclerosis, show perhaps the greatest similarity to my case.

My case differs from Jakob's chiefly in the type of glial reaction. In Jakob's case, the glia cells were preponderantly of the Cajal type, and all of the fatty decomposition products were stored in their cytoplasm. Jakob emphasized the fact that the lowermost two cortical layers were involved. Moreover, the basal ganglia were more severely involved than the cortex.

In Creutzfeld's case, the clinical picture was somewhat different. His patient presented more extrapyramidal motor phenomena. The pathologic picture was obviously more recent and acute and involved chiefly the third and fifth cortical layers, extending as far into the brain

This group of cases may be classified as the "intracortical hemiplegias" of Spielmeyer, Bielschowsky,[29] Hoestermann [30] and Jakob.

---

26. Hallervorden, J., and Spatz, H.: Eigenartige Erkrankung im Extrapyramidalen-System, Ztschr. f. d. ges. Neurol. u. Psychiat. **79**:254, 1922.

27. Jakob (footnote 5, first reference).

28. Creutzfeld, H. G.: Ueber eine eigenartige herdförmige Erkrankung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:1, 1924.

29. Bielschowsky, M.: Ueber Hemiplegie bei intakter Pyramidenbahn, J. f. Psychol. u. Neurol., 1916, vol. 22.

30. Hoestermann, E.: Cerebrale Lähmung bei intakter Pyramidenbahn, Arch. f. Psychiat. **49**:40, 1912.

stem as the nucleus of the fifth cranial nerve; there was, in addition, definite disease of the pyramidal tract.

If lamina III is receptor sensory and the lower cortical layers are effector and motor, a disturbance in the upper cortex interferes with the afferent area of the intracortical reflex arc, thus giving rise to a hemiplegia with an intact pyramidal tract. The cortical pathology gives rise to a functional decortication, "which permits the subcortical ganglia to reign in full sway." Although the changes in the basal ganglia are marked, they are nevertheless far less severe than in the cortex. Because of the widespread pathologic changes it is exceedingly difficult to clarify the clinical symptomatology. The relationship of striatum, pallidum and substantia nigra to the extrapyramidal disturbances in movement can in no way be explained by this case. If involvement of the small striatal cells causes chorea (A. Jakob, in accordance with Hunt and Lewy) and a diffuse slight striatal condition gives rise to parakinesis, then in all probability the clinical picture of chorea followed by athetosis and finally by generalized body rigidity and contracture may be explained by the subsequent pallidal disease.

Birth palsies are not all due to hemorrhage. There is no doubt that hemorrhage or injury does play an important part in certain cases, but there are also cases in which an active process is present. Only further pathologic study will clear this problem.

It must be emphasized that hemorrhage could not have played any rôle in the production of this process, for such a pathologic picture is not that of hemorrhage or its sequelae.

It is now recognized that such widely different causes as cerebral maldevelopment, microgyria, pachygyria, tuberous sclerosis, porencephaly, infantile amaurotic idiocy of Tay-Sachs, Merzbacher-Pelizaeus disease, infantile cases of diffuse subcortical sclerosis belonging to the group of periaxialis subcorticalis diffusa and the intracortical hemiplegias of Spielmeyer-Bielschowsky may all give rise to a typical clinical picture of this condition.

Moreover, cases in which the cortex as well as the basal ganglia was involved in degenerative processes, conditions such as status marmoratus of Cecile Vogt, status dysmyelinisatus of the pallidum and the cerebral hemiatrophy of Bielschowsky give rise to the picture of birth palsies.

My case does not fall into any known nomenclature. It is a cerebral degenerative "process" of unknown etiology, progressive, but with remissions and exacerbations starting at birth and continuous over many years. It caused the typical triad of the infantile cerebral palsy, motor phenomena, epilepsy and idiocy. This case shows the importance of the observation for progression as a clinical manifestation in the birth palsies. The condition was a processive type of infantile cerebral palsy.

THE CEREBRAL LESIONS IN PURULENT MENINGITIS *

FREDERIC WERTHAM, M.D.
Fellow of the National Research Council
BALTIMORE

During the microscopic examination of the brain of a patient who had died of purulent meningitis, I was surprised to find widespread lesions in the parenchyma of the central nervous system—an observation that I had not been led to expect from the current textbooks on the pathologic anatomy of the central nervous system. A study of a large amount of material and reference to the existing literature on the subject made it evident that by some strange omission the parenchymal lesions in purulent meningitis have been inadequately investigated and described. The purpose of this study is to draw attention to these lesions and their extent and nature and—what is even more necessary—to suggest explanations for their pathogenesis.

Although this study deals only with purulent meningitis and the material is composed only of cases of this type, reference must also be made to tuberculous meningitis because of the overlapping of problems that arise. Comparisons between the two diseases and conclusions by analogy are, of course, possible and fruitful, but for purposes of histopathologic analysis and especially for considerations of pathogenesis, the two diseases have to be separated. For general deductions concerning the pathology of the central nervous system, I consider cases of acute purulent meningitis more significant than those cases of meningitis that are due to a specific tuberculous infection and in which the whole organism is usually involved.

REVIEW OF THE LITERATURE ON PURULENT MENINGITIS, WITH SPECIAL REFERENCE TO LESIONS IN THE SUBSTANCE OF THE BRAIN

In his textbook of pathology, MacCallum [1] mentioned the occurrence of macroscopically visible necroses beneath the inner or outer surfaces of the brain in cerebrospinal meningitis. Concerning histologic lesions

* Submitted for publication, Dec. 20, 1930.

* From the Deutsche Forschungsanstalt für Psychiatrie, Munich, Germany.

1. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1926.

in the substance of the brain, he referred to degenerative changes in the epithelium of the choroid plexus, in the more superficial layers of the cortex, in the roots of the nerves and in the sheaths of the blood vessels after their entry into the brain. The perivascular lymph spaces are often filled with leukocytes.

In Aschoff's textbook on pathologic anatomy, Ernst [2] mentioned that in purulent meningitis the substance of the brain is affected more frequently than is assumed, through the slow progress of the infection along the blood vessels and pial sheaths. An infectious edema and softening result, which he spoke of as meningo-encephalitis. The infection may spread via the fissura transversa and the fissura hippocampi to the choroid plexus, "which carries the infection like a fuse." Cerebral meningitis always progresses quickly (within one or two days) to the cord, especially to its posterior part.

In their discussion of purulent meningitis, Buzzard and Greenfield [3] mentioned disease of the brain substance only by saying that the cortex shows little inflammatory reaction except congestion of the blood vessels and the infiltration of small cells in the adventitial lymph spaces. They expressed the belief that one of the chief reasons why leptomeningitis is one of the most acute and fatal types of infection is the raising of the intracranial pressure by the meningeal inflammation, which in turn leads to a deprivation of the supply of blood in the vital centers. (This view will be discussed later.)

Kaufmann [4] stated that in purulent meningitis the brain is voluminous and heavy; there is edema of the cortex, and hemorrhages may occasionally be found there. The infection may be transmitted via the perivascular lymph spaces to the deeper parts, such as the basal ganglia, and thus an encephalitis may result. The meningitis may spread rapidly from the meninges of the brain to the meninges of the cord. Small encephalitic foci may be found in the marginal zones of the cortex. In epidemic cerebrospinal meningitis and also in other severe types of purulent meningitis, encephalitic foci of infiltration and small hemorrhages may frequently be observed macroscopically. Kaufmann said that if a patient recovers from purulent meningitis the residuals are only scar formation in the meninges and possibly hydrocephalus. This view is prevalent among practically all of the authors who

2. Ernst, P.: Das Nervensystem, in Aschoff, L.: Pathologische Anatomie, Jena, Gustav Fischer, 1928.

3. Buzzard, E. F., and Greenfield, J. G.: Pathology of the Nervous System, London, Constable and Company, Ltd., 1921.

4. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. de Gruyter & Company, 1922.

referred to the pathologic residuals of purulent meningitis, but it would not seem to be correct according to the observations of the present investigation.

Borst [5] stated merely that in purulent meningitis the leukocytic infiltration of the meninges may spread to the adjoining substance of the brain via the adventitial lymph sheaths, thus causing an encephalitis.

Ziehen [6] also stated that the leukocytes enter diffusely into the substance of the brain via the lymph sheaths. In places in which this cellular infiltration cannot be found in the brain substance there is at least edema. Phlebitic processes lead to local thromboses. According to Ziehen, all of these conditions of the substance of the brain can be subsumed under the heading of meningo-encephalitis purulenta acuta. An analogous process may occur in the region of the wall of the ventricles, where purulent destruction of the adjoining substance of the brain may follow destruction of the ependyma. In epidemic meningitis the picture is practically the same; but Ziehen mentioned especially that the longer the process lasts, the more the exudate in the ventricle increases. In cases lasting several months, one finds a hydrocephalus internus, an insignificant opaqueness of the meninges and, here and there, encapsulated exudates. In the cases of patients who have recovered from meningitis, one finds meningitis fibrosa microscopically. As an exception one may find in epidemic cerebrospinal meningitis "hemorrhagic-purulent encephalitic foci" occurring independently and at a distance from the meningitic process. The cells of the cortex may also be affected by the "direct primary influence of the infection," as Faure and Laignel-Lavastine stated.[7]

In a summary of the pathologic anatomy of purulent meningitis, Goldstein [8] mentioned that the superficial layers of the cortex are diseased as a rule and show edema and encephalitic and hemorrhagic foci. Abscesses in the substance of the brain may also be found. Encephalitic, hemorrhagic lesions and small abscesses are mentioned in the summary of the pathologic anatomy of epidemic meningitis.

Körner and Grünberg [9] discussed in great detail the pathologic conditions of the meninges. Concerning the involvement of the sub-

5. Borst, M.: Pathologische Histologie, Leipzig, F. C. W. Vogel, 1922.

6. Bruns, L.; Cramer, A., and Ziehen, T.: Handbuch der Nervenkrankheiten im Kindesalter, Berlin, S. Karger, 1912.

7. Faure, M., and Laignel-Lavastine: Étude histologique de l'écorce cérébrale dans dixhuit cas de méningite, Rev. neurol. **10**:807, 1902.

8. Goldstein, K., in Bergmann and Staehelin: Handbuch der inneren Medizin, Berlin, Julius Springer, 1925, vol. 5.

9. Körner, O., and Grünberg, K.: Die otitischen Erkrankungen des Hirns, der Hirnhäute und der Blutleiter, Munich, J. F. Bergmann, 1925.

stance of the brain, they stated only that in all cases there is an acute encephalitis of the upper layers of the cortex, and that small superficial abscesses may occur.

According to Jakob,[10] the infectious process in purulent meningitis may frequently involve the substance of the brain, either by following along the vessels or by breaking into the substance of the brain diffusely from the pia, whereby leukocytes are scattered in the marginal zone of the cortex. If the meningitis becomes more severe, diffuse meningo-encephalitis or circumscribed abscesses may occur. In purulent meningitis due to pneumococci or anthrax, the changes in the parenchyma are not usually pronounced, except in the vicinity of the infectious foci.

Southard[11] stated that in pneumococcal meningitis "the nerve cells failed to show notable or at any rate constant changes." He found an increase of neuroglia cells in the superficial layer. In most cases the cortex was penetrated by polymorphonuclear leukocytes. The vessels of the cortex showed leukocytic infiltration in the adventitia. In discussing streptococcal meningitis, he drew especial attention to the early fibrillary gliosis. It is possible that he did not sufficiently consider the varying normal picture of glia fibers.

Traumatic cases of purulent meningitis in which there are shot wounds in the substance of the brain, with subsequent encephalitic changes and the formation of abscesses, present problems different from those of this study. Ghon[12] discussed such cases. He mentioned two differences between cases in which meningitis follows gunshot wounds and nontraumatic cases; in the former cases, infection with *Staphylococcus pyogenes* and mixed infections with two or more kinds of bacteria occur more often than in the latter. Ghon, following Schottmüller, preferred to call cases of epidemic cerebrospinal meningitis, meningitis Weichselbaum, a name that has not become current. In such cases he mentioned the existence of "encephalitic foci."

---

10. Jakob, A.: Normale Anatomie und Histologie und allgemeine Histopathologie des Grosshirns, Leipzig, Franz Deuticke, 1927.

11. Southard, E. E., and Keene, C. W.: A Study of Brain Infections with the Pneumococcus, Neuropathological Papers, Harvard University Medical School, 1905. Southard, E. E., and Stratton, R. R.: A Study of Acute Leptomeningitis (Streptococcus Pyogenes), Neuropathological Papers, Harvard University Medical School, 1906-1907.

12. Ghon, A.: Zur pathologischen Anatomie der Meningitis Weichselbaum und ihrer Diagnose, Prag. med. Wchnschr. **36**:387, 1911. Ghon, A., and Roman, B.: Zur Klinik, Genese und Aetiologie der eitrigen Meningitis im Kriege, Med. Klin. **11**:1093, 1915. Ghon, A.: Aetiologie der eitrigen Meningitis, Deutsche med. Wchnschr. **42**:244, 1916; Meningitis, Handbuch der aertzlichen Erfahrungen im Weltkrieg, Leipzig, Johann Ambrosius Barth, 1921, vol. 8.

In an experimental study of purulent meningitis in dogs and cats, Streit [13] mentioned incidentally the occurrence of "inflammatory processes in the cerebrum" and cerebral softening as consequences of severe inflammation in the upper layer of the brain.

On the basis of his experimental and pathologic studies, Homén [14] stated that the involvement of the nervous parenchyma in purulent meningitis is insignificant. He mentioned slight edema of the subpial layer of glia, slight progressive changes in the glia cells of the first cortical layer and the immigration of leukocytes from the meningeal infiltration to the marginal zone of the cortex.

In a recent series of papers on experimental meningitis, Stewart [15] discussed the pathology of pneumococcal meningitis in rabbits and dogs. As observations he mentioned only empyema of the central canal of the cord, with destruction of the ependyma and involvement of the underlying substance of the cord, superficial encephalitis, more deep lying infectious foci and hemorrhages. In dogs he found invasion of the choroid plexus, superficial encephalitis and spread of the infection via the Virchow-Robin spaces and myelitis through infection by the perivascular route. He stressed that pneumococcal meningitis in dogs closely resembles that in man. The following lesions of the cord in dogs are described in a special paper: infiltration of the region of the commissures, perivascular infiltration and severe suppurative myelitis. Stewart emphasized the fact that similar conditions of pneumococcal meningitis in human beings must be very rare or unnoted. In his paper on experimental meningitis in dogs infected with type II pneumococci, he spoke of parenchymal necroses which he believed to be due to the "action of a diffusible toxic substance." He found that thrombosis of vessels might lead to parenchymatous softening with subsequent infection and the formation of abscesses.

---

13. Streit, H.: Ueber die Reaktionen der Hirnhäute gegenüber Reizen bakterieller Art, Abhandl. d. Kaiserl. Leopold-Carol. Deutsche. Akad. d. Naturforsch. 1912, vol. 47, no. 7.

14. Homén, E. A.: Experimentelle und pathologische Beiträge zur Kenntnis der infektiös-toxischen meningealen Veränderungen, Arb. a. d. path. Inst. zu Helsingfors **2**:225, 1921.

15. Stewart, F. W.: Local Specific Therapy of Experimental Pneumococcal Meningitis: I. Experimental Pneumococcal Meningitis in Rabbits, J. Exper. Med. **46**:391, 1927; II. The Production, Pathology and Treatment of Type I Pneumococcal Meningitis in Dogs, ibid. **46**:409, 1927; III. Incidental Myelitis Abscess and Organization of Exudates, ibid. **47**:1, 1928; IV. Type II Pneumococcal Meningitis in Dogs, ibid. **47**:515, 1928.

I have found only one paper devoted to parenchymal lesions in purulent meningitis;[16] it was written by Sittig[17] from the psychiatric clinic of Pick in Prague, in 1918. He described a case of epidemic cerebrospinal meningitis in which he found "focal clearings of ganglion cells" (Lichtungen) in the cortex in only one place in the brain, namely, the left temporal lobe. Between these clearings, where no ganglion cells were stained, he found little heaps of intact ganglion cells—with the result that in this place the cortex had a spotty appearance when viewed under a low magnification. From the form and nature of the lesions, Sittig concluded that they are of toxic origin. He referred to Lotmar's studies on the influence of dysentery toxin on the central nervous system[18] and cited a photograph given by Lotmar to show small clearings in the cortex. Sittig expressed the belief that the lesions that he described were of the same nature as those depicted by Lotmar, but of a more pronounced and conspicuous form. After examining the photomicrograph of the lesion described by Sittig (table 4, fig. 1), I was not convinced by his interpretation. I believe that this figure represents a configuration of the cortex that is normal in this region of the brain, namely, the area uncinata. This error is understandable since it occurred at a time when the observations of cyto-architectonics were not currently known and used by histopathologists. But it seems necessary to correct this statement because it is cited in current textbooks. In a review of the pathologic anatomy of epidemic meningitis in the last edition of Oppenheim's textbook of nervous diseases,[19] attention is drawn to the "spotty ganglion cell clearings in the upper cell layers of the left temporal lobe" which were described by Sittig. In the recent handbook of psychiatry edited

16. I omit earlier references on the subject which in the present context have only historical significance, e. g., Klebs' work on the pathology of epidemic meningitis (Virchows Arch. f. path. Anat., 1865, vol. 34). Faure and Laignel-Lavastine (footnote 7) seem to have been the first to investigate the finer changes of the cerebral cortex in meningitis with appropriate methods. Their material was composed largely of tuberculous meningitis. They found parenchymal changes in the immediate vicinity of the meningeal infiltration, which became more pronounced with longer duration of the meningitis.

17. Sittig, O.: Ueber das Vorkommen von fleckweisen Destruktions-Prozessen bei epidemischer Cerebrospinalmeningitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **33**:294, 1916.

18. Lotmar, F.: Zur Wirkung des Dysenterietoxins auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:345, 1912; Beiträge zur Histologie der akuten Myelitis und Encephalitis sowie verwandter Prozesse auf Grund von Versuchen mit Dysenterietoxin, Histol. und histopath. Arb. ü. die Grosshirnrinde **6**:245, 1913.

19. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, revised by von R. Cassiren, K. Goldstein, M. Nonne and B. Pfeiffer, Berlin, S. Karger, 1923.

by Bumke, Weimann[20] also quoted these observations of Sittig in his description of purulent meningitis.

WHY WIDESPREAD PARENCHYMAL LESIONS IN PURULENT MENINGITIS HAVE BEEN OVERLOOKED

According to the more or less uniform views expressed in the literature, therefore, there are no marked parenchymal lesions in purulent meningitis beyond the progress of the infectious process itself to the adjoining substance of the brain or cord, either directly or by way of the adventitial sheaths, depending on the intensity of the infection. Since, however, according to the results of this study, marked and extensive lesions apparently do occur, one must attempt to account for the fact that they have been overlooked. A number of factors may be adduced. In the first place, most emphasis has been put on bacteriologic specificity and differentiations. Then, since meningitis is primarily a disease of the coverings of the brain, textbooks treat it in the chapter devoted to that part of the nervous system, separate from considerations of the substance of the brain itself. The most usual stimulus of neuropathologic inquiry, the question of localization, seemed absent in purulent meningitis. For the diffuse involvement of the brain precludes to a large extent the emergence of isolated neurologic phenomena, while the general mental befuddlement of the patient makes it difficult to consider more specific disturbances of behavior. Any focal phenomena that are present clinically are apt to be covered up by the severe general manifestations of the disease. Further, since purulent meningitis has generally been regarded as belonging to the sphere of the general pathologist, cases have rarely been examined with the special methods of neurohistology. With the usual hematoxylin-eosin stain these conditions of the nervous parenchyma can scarcely be seen.

Even more important, however, than the question of technic seems to be the reason that until recently there has been a general neglect of the circumscribed or diffuse conditions of the nervous parenchyma which lead only to a pale appearance of the region affected, with more or less characteristic changes in the nerve cells and with varying behavior of the neuroglia. The studies of Spielmeyer and his associates on the effects of circulatory factors on the central nervous system have taught one to observe and evaluate correctly these paled areas (Erbleichungen). Formerly such lesions were apt to be overlooked or regarded as artefacts, while in the cases in which there were

20. Weimann, in Bumke, O.: Handbuch der Geisteskrankheiten, edited by W. Spielmeyer, Berlin, Julius Springer, 1930, vol. 11, p. 101.

circulatory disorders, such as hypertonia, the central nervous system was not adequately studied. In cases of apoplexy, for instance, only the site of the main lesion, and perhaps its immediate vicinity, was examined—under the stimulus of the localization of isolated functions. Moreover, histopathologic examination of those parts of the brain in which such lesions are most frequent was often omitted. There is no occasion to go into these studies in detail, but, by way of illustration, their effect on the development of knowledge concerning the parenchymal lesions in tuberculous meningitis may be sketched briefly.

DEVELOPMENT OF THE HISTOPATHOLOGY OF TUBERCULOUS MENINGITIS AS AN EXAMPLE OF THE SIGNIFICANCE OF SO-CALLED PALED AREAS

In general, the histopathologic picture of the encephalitic disorders that may accompany tuberculous meningitis has been well known for a long time.[21] For my purpose, however, only the nonencephalitic lesions of tuberculous meningitis, or at least only those of doubtful encephalitic nature, have to be considered. In 1914, Wohlwill[22] described localized necroses with ameboid glia in the substance of the brain, not restricted to the upper layers of the cortex directly beneath the heavy infiltration in the pia. He thought that they might have a toxic etiology. In the same year, Sittig[23] reported on focal lesions in tuberculous meningitis and enumerated the following types which had been described: (1) intracerebral tubercles, (2) encephalitic foci, occurring through transmission of the meningitic process to the outer layers of the cortex, (3) hemorrhages and (4) softenings through circulatory disturbance. In eleven cases of tuberculous meningitis small clearings in the cortex were found; they were characterized by shrinkage and the dropping out of ganglion cells and regressive changes in the glia. The foci were very sparse. Sittig expressed the belief that they were of toxic origin, basing this view on Lotmar's experiment with dysentery toxin. Fieandt[24] described "analogous foci" and interpreted them as being of circulatory origin. In a paper pub-

21. Spielmeyer, W.: Zur anatomischen Differentialdiagnose der Paralyse, Zentralbl. f. Nervenh. **29**:425, 1906. Ranke, O.: Beiträge zur Lehre von der Meningitis tuberculosa, Histol. u. histopath. Arb. ü. die Grosshirnrinde **2**:252, 1908.

22. Wohlwill: Ueber die amöboide Glia, Virchows Arch. f. path. Anat. **216**: 468, 1914.

23. Sittig, O.: Ueber herdförmige Destruktionsprozesse im Grosshirn und Veränderungen im Kleinhirn bei tuberkulöser Meningitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **23**:511, 1914.

24. Fieandt, H.: Beiträge zur Kenntnis der Pathogenese und Histologie der experimentellen Meningeal- und Hirntuberkulose, Berlin, S. Karger, 1911.

lished in 1920 but completed in 1914, Grafe and Gross [25] mentioned—more incidentally—foci to which they referred as "light empty gaps" in the parenchyma. The vessels, in which the endothelial and adventitial cells show changes, can be seen in these gaps. Between the vessels there is little glia, and it is mostly progressively changed. The lesions extend throughout the cortex and into the adjoining white substance. They are surrounded by a broad zone of protoplasmic glial proliferation. Grafe and Gross used the term "area of softening" for these lesions without going into the question of their pathogenesis.

In 1921, in a paper on tuberculosis of the central nervous system, Kirschbaum,[26] published observations on focal lesions. He spoke of foci that are "free from cells." They resembled those mentioned by Grafe and Gross, but did not have a marginal zone of protoplasmic glia. Instead, they went over directly into cortical layers rich in cells. Kirschbaum considered that these foci were of toxic origin and referred to Dürck's view that areas of softening in malaria are due to the toxic influence of the malarial infection. Jakob discussed disorders of the nervous parenchyma in the first part of his special histopathology.[27] He distinguished lesions due to circulatory factors, encephalitic phenomena and "pure degenerations of the parenchyma." As lesions due to circulatory changes he cited only the consequences of thromboses and breaks in the walls of the vessels. The degenerative changes consist in the involvement of the marginal zones of the cortex and in diffuse and localized clearings in the cortex. He also considered that foci of the nature of those described by Sittig are of toxic origin. He mentioned further that far from the tuberculous infiltrations localized proliferation of the glia may occur, in the cornu ammonis and in the molecular zone of the cerebellum; he did not commit himself as to the nature of the process.

That thromboses of small pial vessels may lead to "anemic foci of softening" apparently has been noticed frequently. Nathan [28] recently published a report of several cases to show that in tuberculous meningitis, aside from the small and medium arteries of the brain, the major arteries at the base of the brain may show specific inflamma-

25. Grafe, E., and Gross, W.: Ueber einen ungewöhnlichen Fall von Conglomerattuberkulose des Gehirns (Sitz des Haupttuberkels am unteren Ende der Medulla oblongata), Ztschr. f. d. ges. Neurol. u. Psychiat. **57**:259, 1920.

26. Kirschbaum, W.: Ueber die Tuberkulose des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **66**:283, 1921.

27. Jakob, A.: Spezielle Pathologie des Grosshirns, Leipzig, Franz Deuticke, 1929.

28. Nathan, H.: Blande anämische Erweichungsherde im Anschluss an eine infektiöse Thrombarteriitis (tuberculosa beziehungsweise purulenta) grosser Hirnbasisarterien, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:579, 1930.

tory changes. Such changes may lead to foci of anemic softening without inflammation. Spielmeyer [29] demonstrated that in tuberculous meningitis small clearings may occur in the nervous parenchyma as a result of endarteritic and endophlebitic changes, in parts of the brain such as the cornu ammonis. On the basis of his work an extensive investigation of focal lesions in tuberculous meningitis was undertaken by Bodechtel and Opalski.[30] They studied thirty cases of tuberculous meningitis, and in practically all of them they found numerous parenchymal changes, paled areas and clearings, especially in the cortex, but also in the deeper gray structures. They referred to analogies with purulent meningitis. From a consideration of the nature of the lesions, they claimed that the widespread necroses in the substance of the brain are independent of the meningo-encephalitic process, except so far as it affects the blood vessels, and are due to circulatory disorders. They denied the "toxic" etiology of such lesions, which had been assumed by previous authors. It is not necessary in this connection to go further into the pathology of tuberculous meningitis.

MATERIAL AND METHODS OF INVESTIGATION

The material of this investigation consisted of twenty-four cases of purulent meningitis of various types.[31] It is not necessary for the purposes of this study to give in detail the clinical data and the observations at autopsy in these cases. The ages of the patients ranged from 2 months to 66 years; there were ten adults and fourteen children. In all cases the diagnosis was verified—or established—at autopsy. Bacteriologic examination revealed the following kinds of organisms: pneumococci, meningococci, diplococci (not specified), mixed cocci, streptococci and *B. coli*. The material was fixed partly in formaldehyde and partly in alcohol. The following methods of staining for histologic examination were used: Nissl, cresyl violet, hematoxylin and eosin, Spielmeyer's unembedded myelin sheath stain, Herxheimer's fat stain, Bielschowsky's neurofibril stain, Holzer's glia fiber stain, the Kulschitsky-Wolter stain for myelin sheaths on embedded material, the van Gieson stain, Weigert's fibrin stain, Weigert's elastica stain, Hortega's microglia method (on material fixed in bromide-formaldehyde) and the Turnbull iron reaction. Serial sections were made of some of the necrotic foci. These methods were applied to the material in varying intensity in the individual cases. A report of all of the histopathologic observations in each case would be too cumbersome, as well as unnecessary for the main points to be demonstrated.

---

29. Spielmeyer, W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:5, 1925; Die Pathogenese des epileptischen Krampfanfalles, ibid. **109**:501, 1927.

30. Bodechtel, G., and Opalski, A.: Gefässbedingte Herde bei der tuberkulösen Meningitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:401, 1930.

31. Most of these cases were observed in the Schwabing Hospital, and the histopathologic examination of the central nervous system was made possible by the director of the department of pathology, Professor Oberndorfer.

Macroscopic Appearance and Observations in the Meninges.—The macroscopic appearance of the meninges will not be discussed in detail. Considerable space is given to this subject in papers and textbooks, and my detailed observations on dissection of the brain would be largely a repetition of well known facts: the thick infiltration of the meninges, which favors the convexity, but by no means so exclusively as has sometimes been stated; the collection of purulent matter in the large cisternae, the occurrence of a mild hydrocephalus internus, etc.

As to the nature of the exudate, it was striking in most cases that microscopically the thick leukocytic infiltration did not reach as far as the substance of the brain, but was separated from it by a sharply defined layer, composed mainly of macrophages and other basophilic round cells. Corresponding areas also occurred around vessels in the meninges. Macrophages may appear early, even

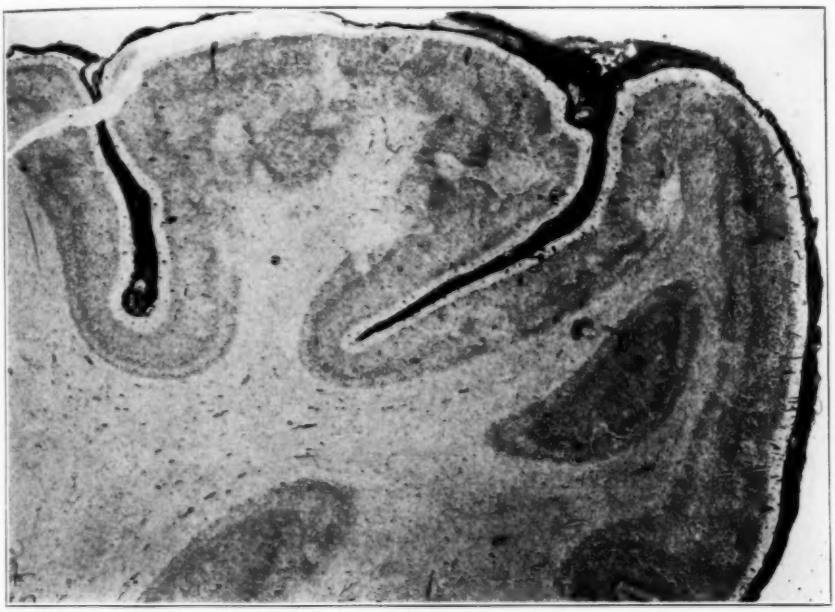


Fig. 1.—Cortex showing numerous scattered paled areas. Purulent meningitis of three days' duration in a child, aged 5½ months. Nissl stain.

when the meningitic process has lasted for less than three days. A pronounced exudation of fibrin frequently occurs. A layer of infiltration near the substance of the brain may become necrotic early; that is, even if the duration of the meningitic process is less than three days. With the fibrin stain the following layers could be distinguished: the layer of fibrin exudate, a necrotic layer of infiltration and above that the masses of leukocytes and basophilic round cells. In many cases another detail that was striking microscopically was a ring of leukocytes that encircled the blood vessels in the meninges, but were found at a definite distance from the walls of the vessels; this is apparently due to a perivascular edema that keeps the leukocytes at a distance.

Ependymal granulations such as occur in infectious diseases of the central system were observed in several cases.

Occurrence and Distribution of Parenchymal Lesions.—In the majority of cases, paled areas can be seen in sections stained with the Nissl stain, if they are viewed with the naked eye against a white blackground. In fact, when one looks at the sections through the microscope, one may miss these necrobiotic places, as they stand out more clearly with little or no magnification. They show as discrete patches stained less intensely than the surrounding tissue against which they are sharply delimited (figs. 1 and 2).

In many instances these paled areas are near the places where there is a pronounced meningeal infiltration. In such cases the cortex

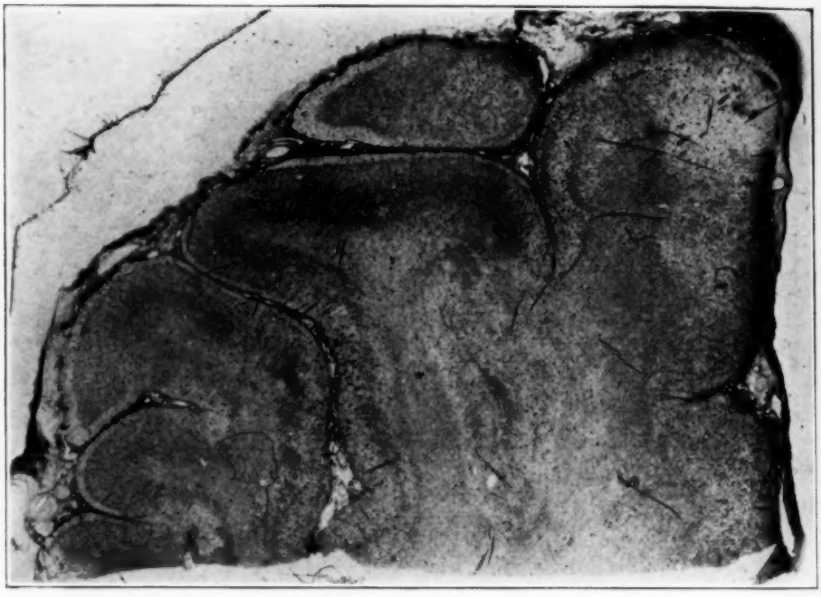


Fig. 2.—Paled areas in the cortex, with beginning softening and proliferation of the vessels. The normal white matter stained more deeply than the pale necrobiotic cortex. Purulent meningitis. Nissl stain.

is affected either on the crest of the gyrus or, often to a more severe degree, in the region where it surrounds the bottom of the sulcus. It is difficult to account for the frequency of especially pronounced paled areas in the immediate region of the sulci. The infectious exudate is apparently marked in the meninges that descend into the sulci, as compared with the meningeal covering of the crest of the gyri. Borst, who also mentioned the occurrence of more pronounced infiltration in the sulci, expressed the belief that it is due to the fact that the subarachnoid spaces are much more strongly developed in the sulci than they are over the crests of the gyri, which allows more space for exudate in the

sulci. It is possible that this impression of a better development of the subarachnoid spaces in the sulci does not correspond to the actual relationship in the living organ, but that it is based on the effect of the fixation of the material on the surface of the brain. The severity of the paled areas in the region around the sulci can be demonstrated frequently; for this no adequate explanation is available. Exceptions to this rule do occur, however.

In addition to this group of lesions that lie near the site of the meningeal infiltration, there are also paled areas at a distance from the meninges; for example, in the deeper layers of the cortex, the white

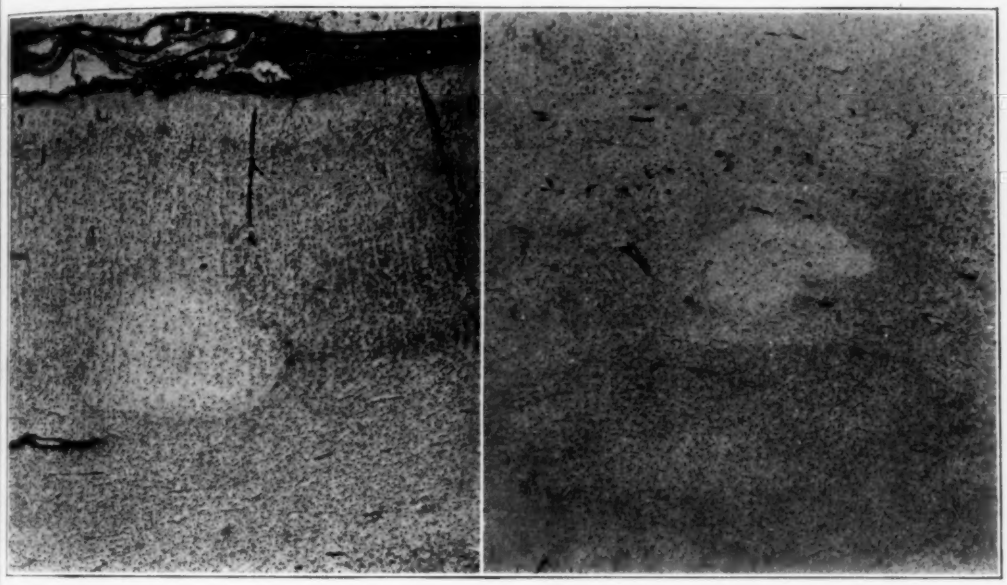


Fig. 3.—The photomicrograph on the left shows a paled area in the deeper layers of the cortex which reaches into the white matter; that on the right, a paled area in the white substance just above the subthalamic body. Nissl stain.

substance and the basal ganglia. Figure 3 shows a paled area in the deeper layers of the cortex, reaching to the white substance, and a similar lesion in the white substance just above the corpus luysii. In figure 4 there are paled areas in the putamen, the caudate, the internal capsule and the claustrum. The diffuse paling of the cortex may be so marked that in such a gyrus as is shown in figure 2, the white substance may appear distinctly darker than the cortex, although the former shows no increase in nuclear elements or any other pathologic change. The paled areas (Erbleichungen) in these two large groups which one might distinguish from a formal point of view, namely, lesions near the meninges

and those at a distance from the meningeal infiltration, are not only similar in their characteristics, but are identical. They are usually clearly outlined, but may be either localized or more diffuse.

HISTOLOGIC DETAILS OF THE OBSERVATIONS

Such changes as have already been mentioned can be seen with the naked eye or with slight magnification. Microscopic examination reveals many other pathologic features in the substance of the brain. Of these the finer microscopic changes in the paled areas visible to the naked eye will be taken up first.

Fig. 4.—Marked palings in the putamen, caudate, internal capsule and claustrum. Purulent meningitis of from three to four days' duration in a child, aged 5 months. Nissl stain.

Within such a lesion a large number of nerve cells and glia cells have apparently disappeared. Other cells are pathologically changed. Some nerve cells may be very pale, either with a hemogeneous pale blue tinge (Nissl stain) or with smaller dark granules. Other cells are shrunken and darkly stained with pyknotic nuclei. Less characteristic changes are also seen. Some cells show the ischemic type of pathologic nerve cell change which has been described by Spielmeyer. The most pronounced form of this change is especially seen on the border and in the neighborhood of the paled areas. There, also, cells can be found that show changes similar to the "severe type" of cell change described by Nissl and the "homogeneous" type of cell change first described for the Purkinje cells. Many nerve cells have "dropped out." The glia cells that are left show

regressive changes. Frequently they are darkly stained, but sometimes they are pale and hardly distinguishable. Apparently a progressive reaction of the glia may set in very early. This progressive reaction of the glia, however, seems dependent not only on the age of the lesions, but also on their location. This is particularly manifest, for instance, in the cornu ammonis, where an enormous proliferation of microglia frequently occurs. This is well brought out with the Hortega microglia stain, but it can be clearly seen with the Nissl stain. Besides the proliferaton of the microglia in the Sommer sector of the cornu ammonis, large progressively changed fibrous glia cells are also found.

Quite apart from the actual dropping out of nerve and glia cells, the appearance of these paled areas is also due to the fact that the underlying tissue in which the cellular elements are embedded has lost the hue that it normally shows in a

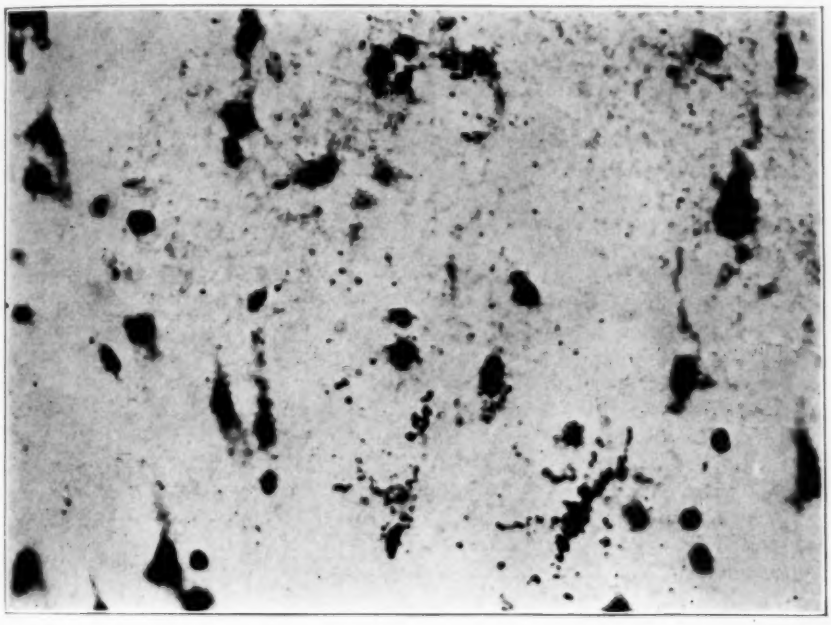


Fig. 5.—High power view of a section from an area of extravasation of blood in the frontal cortex. Pneumococcal meningitis following influenza. The photomicrograph shows microglia cells the processes of which are outlined with pigment granules. Nissl stain.

stained preparation. Within these areas the blood vessels stand out darkly. This is due not only to adventitial infiltration, but much more to a thickening of all of the walls of the vessels, especially those of the intima and the adventitia.

Under the microscope it is also evident that there are many smaller clearings in the cortex, which are best found under low magnification. Sometimes several layers are involved; sometimes one layer is predominantly affected. The second and fourth layers of the cortex seem to be least affected, although clearings may be found which involve the second and third layers equally. In the same way, clearings in the third or fifth layers may reach definitely into the fourth.

The areas of "red softening" are of special pathologic interest. They do not seem to be frequent in purulent meningitis, although they do occur. Bodechtel and Opalski [30] have expressed the opinion that in tuberculous meningitis the red blood corpuscles found in the substance of the brain may be due to agonal circulatory disorders. The primary lesion is a white softening into which an extravasation occurs during the terminal stage. Sometimes it is not easy to decide whether such extravasations are agonal or preagonal. Figure 5 shows a region of diffuse extravasation in the frontal cortex. This case occurred in a baby, aged 5 months, in whom meningitis developed following influenza. Pneumococci were found. In the cortex there were small confluent areas where red blood corpuscles could be seen outside the walls of the vessels. Near these extravasations pigment could be seen with the Nissl stain. Microglia cells, the processes of which were outlined by granules of pigment, could be discerned (fig. 5). The Turnbull iron stain did not prove definitely that this was iron-containing blood pigment. Since the material had been one day in formaldehyde before it was embedded, it is possible that this pigment is of the type of formaldehyde-determined precipitate that occurs frequently near vessels filled with blood or near extravasations, even when the rest of the preparation does not contain precipitates. My impression is, however, that these extravasations occurred intra vitam. If this is correct, the observation of these extravasations would be of interest for considerations of pathogenesis of cerebral lesions in meningitis, as they are a direct evidence of intracerebral vascular changes.

Alterations of the nerve cells may occur diffusely and not in a definite connection with focal clearings. Ischemic changes of nerve cells are especially conspicuous and clearly demonstrable. In the third layer, for example, stretches of large pyramidal cells, all of which show the ischemic cell change in its most pronounced form, can be seen. Other cells stain poorly in the Nissl picture; the Nissl substance is no longer distinct, and the nucleus is darkly stained or shows other pathologic changes. Cells are frequently observed that show the "severe type" of cell change of Nissl and other similar changes. The cell is swollen, and its protoplasm is homogeneous, without Nissl bodies; there are small vacuoles diffusely scattered in the cell body; the nucleus is small and shows marked hyperchromatosis. All of these changes occur most frequently in the vicinity of the regions with paled areas.

The fat picture brings out interesting changes in some cases. It is of considerable interest that much fat may be found very early in intense processes. This was shown in the case of a patient, aged 18, who for seven months suffered from an osteomyelitis of the roof of the cranium. Despite several operations, the condition progressed. "Small brain abscesses" over the left and right mastoid were opened. Three and one-half days before death, an elevated temperature, pains in the nape of the neck and somnolence suddenly developed. Paralysis of the right arm followed, and later aphasia and paralysis of the whole right side occurred. Kernig's symptom was present. The spinal fluid was opaque and contained numerous leukocytes. There was papilledema. At autopsy an extensive purulent meningitis of the convexity of the brain was shown, especially marked on the left side. In regions of the cortex where the pial infiltration was marked, the ganglion cells were found to be laden with fat. In the same case much fat was observed in the blood vessels of the pia. The Nissl stain showed the presence of innumerable scavenger cells in the upper layers of the cortex. In the Herxheimer fat picture they were particularly conspicuous; the mass of these cells crowded with large bright red fat globules gave the whole upper part of the cortex a most striking appearance.

The cerebellum is frequently involved, and the Purkinje cells may show marked changes. The whole cell body is often diffusely stained, either a very pale or a very dark blue (in the Nissl picture). Characteristic forms of the so-called homogeneous cell change are frequently found.[32] In connection with the change in the Purkinje cells there may be a proliferation of the Bergmann layer of glia cells of varying intensity. Glial formation of the nature of shrubbery formation (Strauchwerk) was observed in some cases. In one case the changes in the cerebellum were marked. This case was one of diffuse, purulent meningitis following a right-sided otitis media, occurring in a child, aged 2. The meningitis lasted for five days. There were thromboses in the right sigmoid sinus, and a slight hydrocephalus internus was noted. In one region of the cerebellum there was a local atrophy of the lobules. The cerebellum also showed softening and

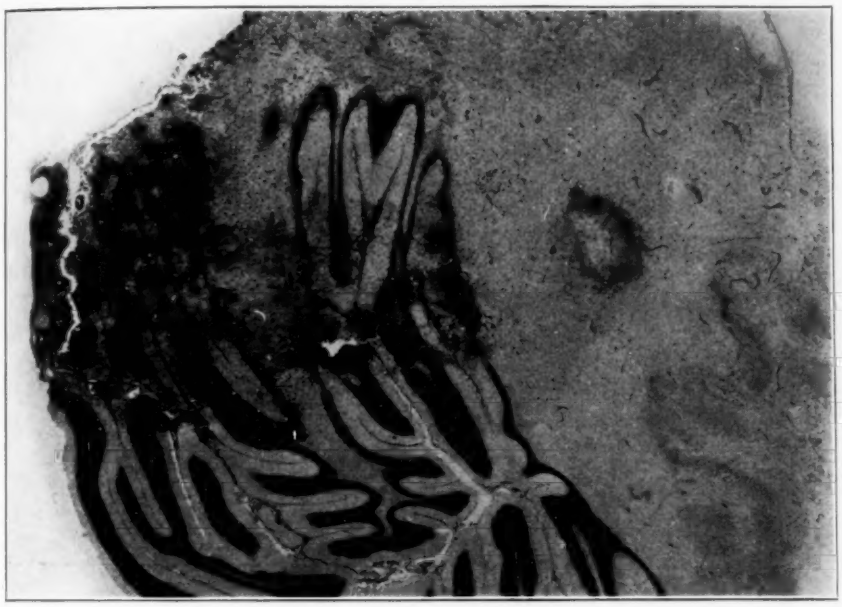


Fig. 6.—Abscess formation in the cerebellum in a case of purulent meningitis. The structure of the cerebellum can still be recognized in the involved area. Nissl stain.

invasion by leukocytes, with necrosis and proliferation of the blood vessel-connective tissue apparatus (fig. 6). The tissue contained macrophages and scavenger cells. In the molecular zone in the vicinity of the abscess, diffuse glial proliferation and proliferation of the blood vessels were seen. This same case showed pathologically changed Purkinje cells of the homogeneous type. In the olives there were small clearings formed by the dropping out of nerve cells. The cortex

32. Brief descriptions of the various types of pathologic changes in the cells mentioned here can be found in English in a recent paper by E. Gildea and S. Cobb. (The Effects of Anemia on the Cerebral Cortex of a Cat, Arch. Neurol. & Psychiat. **23**:876 [May] 1930.)

also showed small clearings, of the type already described, and frequent changes of cells of the ischemic or "severe" type, as well as cells with pericellular incrustations. The cornu ammonis of one side showed definite clearings and marked cells changes in the Sommer sector and in the end-plate. The white matter of the hemispheres showed many vessels with leukocytic cuffing.

The diffuse reactions of the glia were especially marked in the first layer of the cortex. Here the progressive and regressive changes were sometimes striking. The glia nuclei were darkly stained and pyknotic, and often they were broken up or otherwise regressively affected. My first impression as to progressive changes was that the layer of glia fiber at the surface of the cortex was pathologically increased. On closer comparison of sections stained by Holzer's glia fiber method

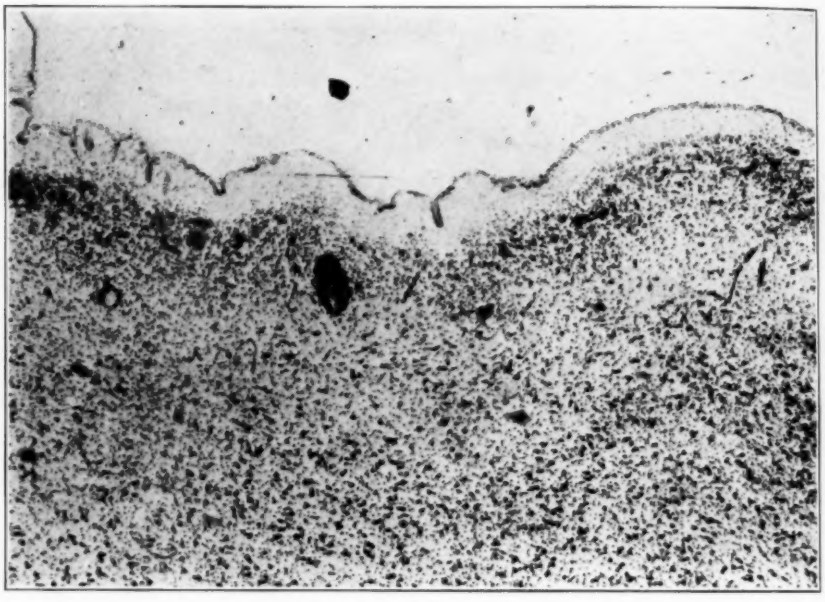


Fig. 7.—Wall-like formation of progressive glia under the surface of the ventricle in purulent meningitis. Nissl stain.

with the classic pictures in the Weigert atlas on neuroglia it became questionable whether this increase in glia fibers was really marked. However, it does seem that there may be such an increase in glia fibers in the depths of the sulci. In one case the network of glia fibers in a sulcus was so woven into the severely diseased meninges that they became united with the substance of the brain. In the Nissl picture, a "wall" of progressive glia could sometimes be seen in the first layer of the cortex. An increase in glia may also occur around the ventricles (fig. 7); I have observed this process in adults as well as in children.

Circumscribed proliferation of glia, either in the form of small clusters of glia or of larger patches such as are shown in figure 8, could be observed in the cortex. Smaller patches also occurred in the first layer (fig. 9). Discrete patches of proliferated glia occurred in other parts of the gray matter as well. A glial reaction in the form of so-called glia clusters in the olives will be discussed later.

The myelin sheath stain is especially useful in demonstrating cerebral lesions in meningitis. Few cases of meningitis, tuberculous or purulent, have been examined with this method. The severe disorders of the cortex shown by the Nissl stain are also brought out in this way. Within the sphere of the more pronounced necroses the radii are destroyed. Over whole stretches of the cortex the radii are diffusely affected and appear as though they had been shaved off. In the myelin sheath pictures it is again conspicuous that the sulci are more severely affected than the tops of the gyri. In some places the myelinated fibers are swollen and tortuous. Frequently, the myelo-architectonics of the cortex is disorganized. In the white matter, especially in the superficial parts and at the junction of the cortex and the white matter, there are small patches of demyelinization.

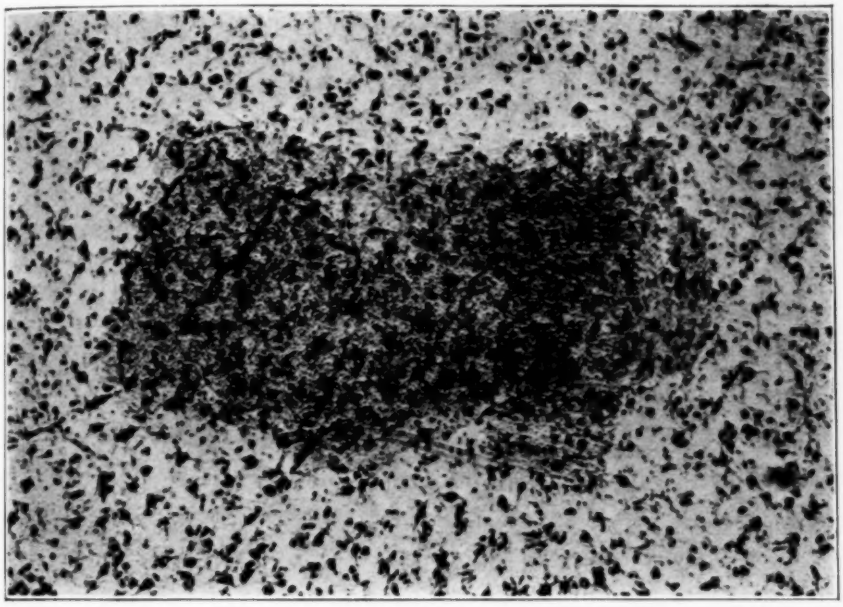


Fig. 8.—Circumscribed glial proliferation in the cortex. Nissl stain.

That necrobioses may reach from the cortex into the white matter has already been demonstrated with the Nissl stain (fig. 3). The type of patches of encephalitis demyelinization shown in the case in which there was meningitis and encephalitis (fig. 15) do not seem to occur to any extent in the uncomplicated cases of meningitis.

The cornu ammonis and the olives are topographic regions that deserve especial attention. Both of these regions are frequently affected in purulent meningitis. The microglial reaction in necrobioses in the cornu ammonis has already been pointed out. Such reactions may often be found. The paled areas affect the Sommer sector as a whole or in part, and they may occur in the whole length of the cornu ammonis. This was demonstrated by serial sections through the cornu ammonis, which showed that the same paled areas occurred from the anterior through the middle to the caudal area.

The vulnerability of the inferior olives in purulent meningitis is impressive. My observations confirm their vulnerability as found in other conditions as discussed by von Braunmühl.[33] The inferior olives were affected in almost every case. Sometimes a whole portion of the band may drop out; sometimes many ganglion cells disappear, which gives a diffuse appearance to the whole band. One has to be careful, however, in evaluating the pathologic changes of the cells in the inferior olives, because there is a considerable variability in the appearance of these cells normally. The age of the patient has to be taken into account. In one case the cells of the olives were found to contain an enormous amount of lipoid pigment. The nucleus was pushed to the side, and was darkly stained and sclerotic. But as this case occurred in a woman, aged 66, the observation could not be given special significance. Even allowing for all changes due to physiologic

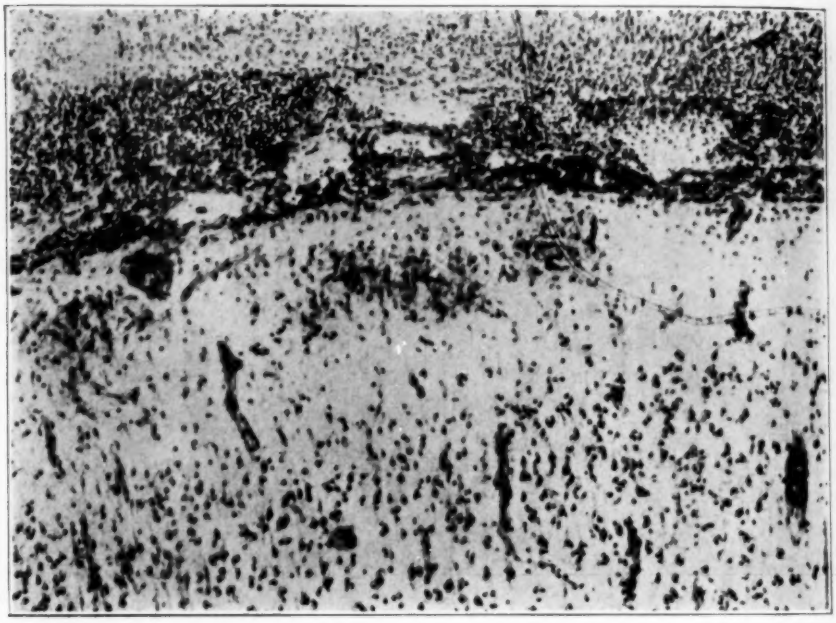


Fig. 9.—Patches of proliferated glia in the first layer of the cortex in purulent meningitis. Nissl stain.

aging, marked pathologic changes were found with extraordinary frequency. There were ischemic cells, homogeneous cells, cells with the "severe cell disease" of Nissl, with or without incrustations and other cells showing less sharply definable changes. Neuronophagia was seen frequently. In one case numerous clusters of glia cells were found (fig. 10). Glial proliferation frequently occurs in the regions

33. von Braunmühl, A.: Zur Histopathologie der Oliven, unter besonderer Berücksichtigung seniler Veränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:213, 1928; Zur Pathogenese örtlich elektiver Olivenveränderungen, ibid. **120**:716, 1929; Ueber Ganglienzellveränderungen und gliöse Reaktionen in der Olive, ibid. **126**:621, 1930.

where the ganglion cells are pathologically changed. The glia nuclei were large, and the protoplasm was plentiful and stained clearly.

In the cases with marked changes in the inferior olives the nucleus dentatus was sometimes affected, but without following any rule. The Purkinje cells of the cerebellum also were frequently affected, but it was not possible to establish a parallelism between the condition of the olives and the Purkinje apparatus.

The encephalitic changes found near the inner or ventricular and the outer surfaces of the brain, namely, near the ventricular system and in the superficial layers of the brain, may be discussed separately. The damage that they do to the nervous parenchyma is not extensive

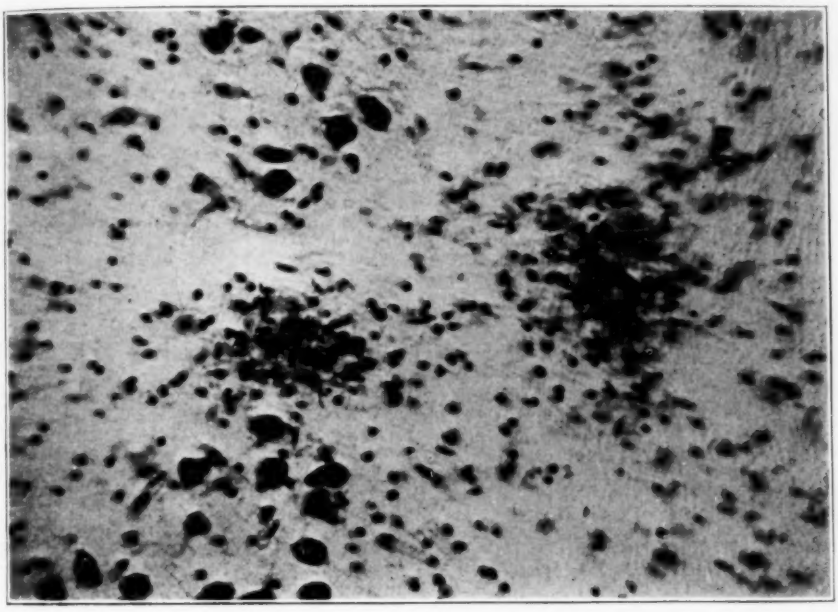


Fig. 10.—Clusters of glia cells in the region of the inferior olives. Nissl stain.

as compared to the previously discussed lesions. They are important, however, for some wider problems of neuropathology.

Near the outer surfaces of the brain an infiltration of the blood vessels with leukocytes frequently occurs. Leukocytes can often be seen diffusely spread over the upper layers of the cortex. It does not seem that this process is due to a diffuse breaking through from the pia through the membrana limitans gliae that plays such an important part in the literature. The leukocytes seem to come mostly from the infiltrated vessels. Their progress from the walls of the vessels to the region around the vessels, where they are less dense, and then to the tissue where they lie scattered loosely, is indicated in the preparations. A glial proliferation may rarely occur in the wall-like formation under the outer surface of the brain. A small patch of such glia is shown in figure 9.

The encephalitic changes on the inner, namely, the ventricular, surface of the brain are more important. They demonstrate clearly that in cases of purulent meningitis a ventricular infection exists. The effects of this ventricular infection on the nervous parenchyma seem to throw light on a current problem of histopathology, namely, that of the Turnbull-Lucksch-Wohlwill type of encephalitis (encephalitis postvaccinationem and encephalitis postmorbillosa).

The blood vessels in the immediate vicinity of the ventricular system are frequently heavily infiltrated with leukocytes. The behavior of the glia is more interesting. One can frequently find a proliferation of the glia in a wall-like formation under the ependymal layer (fig. 7). An interesting feature of this subependymal glial proliferation is the fact that it consists to a great extent of large glia cells, which is also the case in postvaccinal encephalitis. This shows that the type of glial reaction is to a great extent dependent on its particular localization in the central nervous system, and not only on the pathologic process itself. In the evaluation of this subependymal glial proliferation, it is necessary to keep in mind that even normally a considerable amount of glia is to be found in certain places near the ventricles, not only in children but also in adults.

This type of subependymal glial reaction has been considered one of the characteristics of postvaccinal encephalitis. Spielmeyer [34] depicted it in a recent paper on that disease. My observations of this subependymal glia wall in purulent meningitis seem to be the same as those described in postvaccinal encephalitis. In both diseases the process occurs frequently in the subependymal layer and rarely on the outer surface of the brain (subpial layer). Therefore, this predilection for the inner surfaces seems to be not a characteristic of postvaccinal encephalitis, but the result of a general reaction tendency of the central nervous system. The reactions of the glia seem to differ in postvaccinal encephalitis and in purulent meningitis in only three points that are not essential: (1) In the former condition the lateral ventricles are a place of predilection, whereas the fourth ventricle, the aqueduct and the cerebral canal are free. This type of localization does not obtain in purulent meningitis, in which varying parts of the ventricular system may be affected. (2) Heavily infiltrated blood vessels can often be found near the glia walls in purulent meningitis—an observation seemingly rare in postvaccinal encephalitis. (3) Here, the glial proliferation does not seem to go over into a perivenous glia syncytium, as it does in cases of encephalitis following vaccination or measles. The fact that this type of glial proliferation does occur so frequently in purulent menin-

34. Spielmeyer, W.: Die nichteitrige Encephalitis im Kindesalter: Anatomischer Tatsachen und Probleme, Monatschr. f. Kinderh. **44**:195, 1929.

gitis, in which the nature of the bacterial infection is known, has a bearing on the general pathologic problem of inflammation. For if these observations in meningitis are added to the observations in the Turnbull-Lucksch-Wohlwill type of encephalitis, a continuous series of transitions in the reaction of the periventricular tissue to the pathogenic agent in the cerebrospinal fluid can be shown: from the subependymal glia wall without infiltration of vessels and mesenchymal reaction, through the glial proliferation plus inflammatory changes in the vessels to the fully fledged periventricular encephalitis with leukocyte cuffing of the vessels and relatively little reaction of the glia. These transitions show that one cannot regard the glial prolifera-

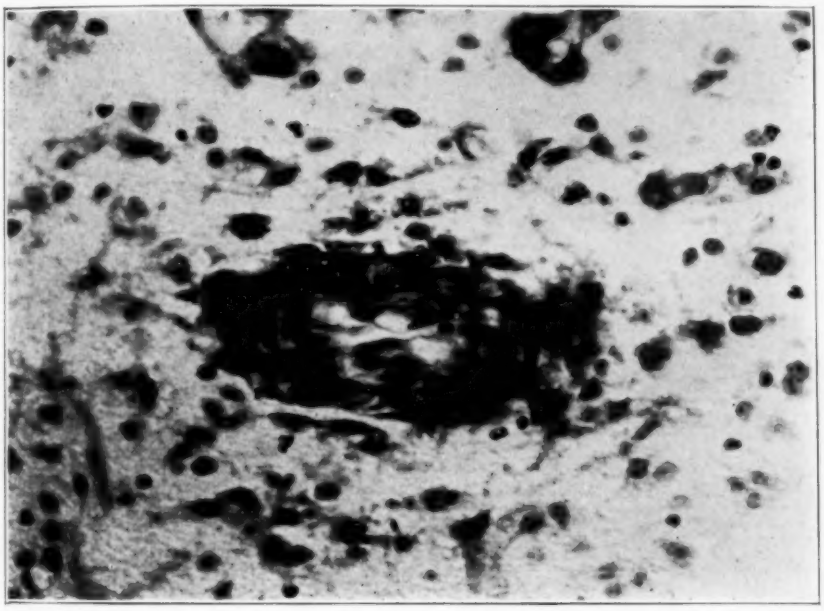


Fig. 11.—Intracerebral blood vessel in purulent meningitis, showing thickened walls and large endothelial cells. Nissl stain.

tion in postvaccinal encephalitis as "noninflammatory." The neuroglia in the central nervous system has functionally the closest relationship to the blood vessel-connective tissue apparatus. These observations on glial proliferation in purulent meningitis also deserve consideration in attempts to distinguish ultrafiltrable and bacteriologic infections of the central nervous system on the basis of the behavior of the glia such as have been made by Pette.[35]

35. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928; Akute Infektion und Nervensystem, München. med. Wchnschr. **76**:225, 1929.

CHANGES IN THE BLOOD VESSELS

In practically all of the cases on which this study is based, meningeal as well as intracerebral vessels were affected. Loewenstein,[36] who also described dissolution of the Nissl granules in ganglion cells of the brain and cord in cerebrospinal meningitis, has described the severe changes of the blood vessels of the meninges in purulent meningitis. In the cases of this study the small vessels of the cortex stood out darkly stained in Nissl preparations. This was due not only to infiltrations, but also to changes in the vessels themselves. The walls were greatly thickened, the endothelial cells being increased both in size and in number[37] (figs. 11 and 12). Both the intracerebral vessels and the meningeal

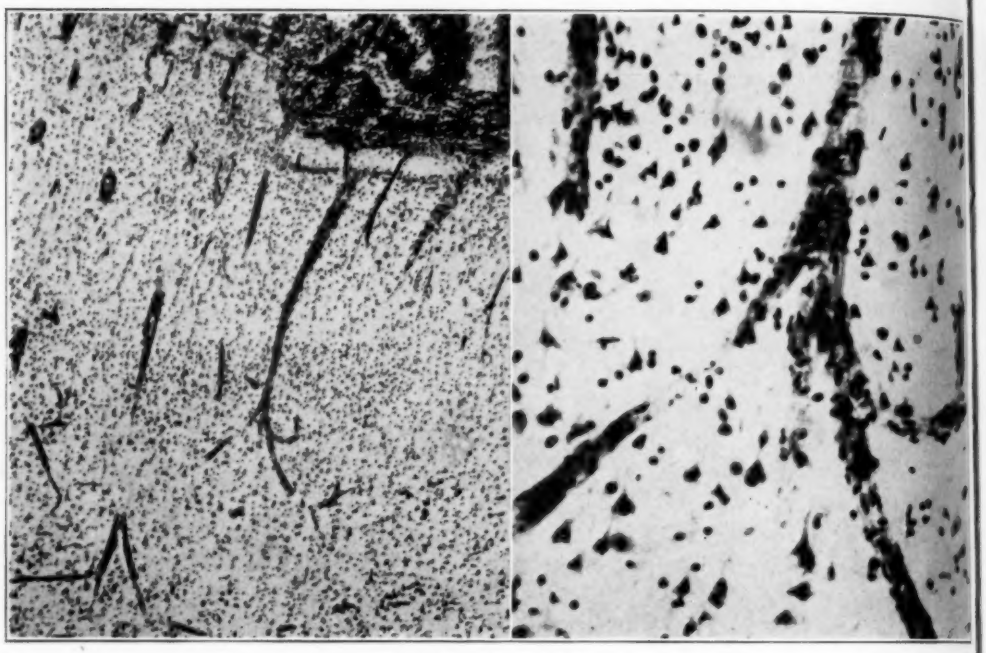


Fig. 12.—Photomicrograph showing how conspicuously the blood vessels stand out in Nissl stains of the cortex in purulent meningitis. This is due to proliferation and increase in the size of the cells in the walls of the vessels and not to perivascular infiltration. The photomicrograph at the right shows part of the largest vessel of the first picture under a higher magnification. Nissl stain.

vessels are usually congested and hyperemic. With the Weigert elastin stain the diseased meningeal blood vessels show up with great clearness. One can see very

36. Loewenstein: Ueber die Veränderungen des Gehirns und Rückenmarks bei Meningitis cerebrospinalis, Beitr. z. path. Anat. u. z. allg. Path. **47**:282, 1910.

37. A discussion of endarteritic changes in small cortical vessels in severe infections has recently been published by Winkelmann and Eckel (Endarteritis of the Small Cortical Vessels in Severe Infections and Toxemias, Arch. Neurol. & Psychiat. **21**:863 [April] 1929).

early stages of degeneration of the vessels in which the elastica interna gives way in only one place, and later stages in which the whole circumstance of the vessel is affected (fig. 13). Thromboses in the vessels can be seen with the fibrin stain. Spielmeyer [38] drew attention to such thromboses of smaller meningeal veins in purulent meningitis, which may cause, as an indirect effect of infection, hemorrhages in the substance of the brain. If one examines areas where small clearings occur in the cortex, it can often be seen that they stand in definite relationship to blood vessels. Sometimes the paled areas assume the wedge-shaped form so frequently found in the vascular lesions of arteriosclerosis and similar conditions, with the tip of the wedge pointing either to the white matter or to the surface. Sometimes both types can be seen in one section. These observations are of significance for the problem of the distribution of the supply of blood in the

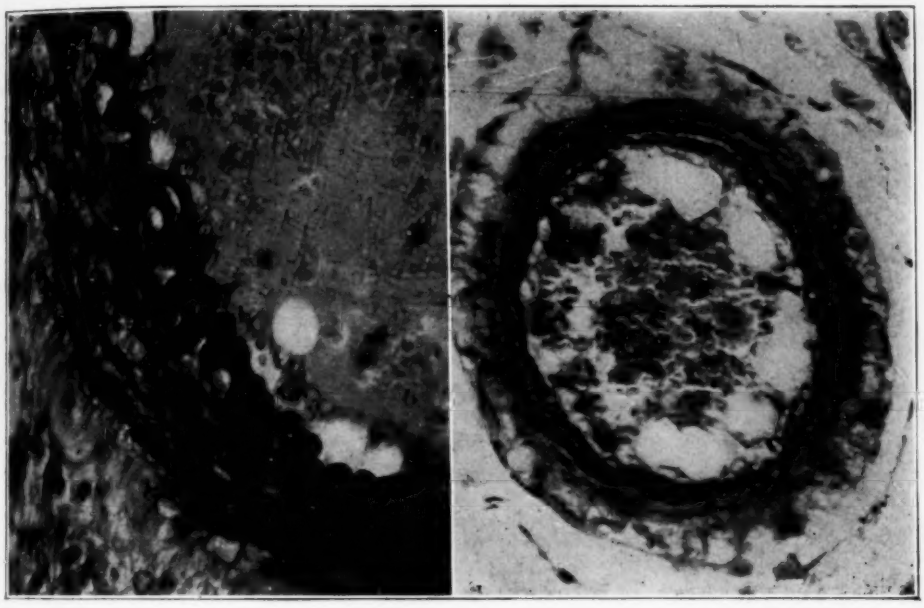


Fig. 13.—The photomicrograph at the left shows part of a blood vessel that seemed fairly intact under low magnification. With a high magnification one can see how the elastica interna begins to yield and that it is split up in one place. On the right is shown a blood vessel in a later state of damage in which the elastica interna is divided into two parts around the whole circumference of the vessel. Weigert's elastin stain. Purulent meningitis in an 18 year old patient.

cortex—a subject that has recently returned to the foreground of interest through the researches of Pfeiffer. A more detailed discussion of the changes of the vessels cannot be given summarily. It would have to take into account not only the different stages of the meningitic process, but also the specific type of bacterial infection.

38. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

Pathogenesis of the Parenchymal Lesions.—A rather mechanical theory prevails as to the pathogenesis of cerebral lesions in meningitis. It is assumed that involvement of the substance of the brain is negligible, and that only with the greater intensity of the infection of the meninges does the infection spread from the surface to the substance of the brain, either along the blood vessels or by a diffuse breaking through. But in reality the circumstances are much more complicated. It is true that the subarachnoid space is morphologically continuous with the adventitial space of the blood vessels, and that it would therefore seem plausible that the infection should progress rapidly from the meninges into the substance of the brain as far as the blood vessels still have adventitial spaces. But, functionally, the two spaces are evidently not a simple continuation. This can be seen even in experiments in which dyes are introduced into the subarachnoid space. The stain will fill the whole subarachnoid space, especially the cisternae. But the Virchow-Robin spaces are stained only in the region near the meninges and not in all their extent into the substance of the brain (Spatz).

The term meningo-encephalitis may be exceedingly misleading. It may express merely a stage of the meningitic process, as there may be evidence of encephalitis, namely, leukocytic cuffing of the vessels in the substance of the brain and the reaction of the surrounding tissue. Such encephalitic foci are responsible for only a small part of parenchymal lesions in meningitis. One may also speak of meningo-encephalitis in cases in which a real diffuse encephalitis exists side by side with a meningitis. In one case in this study such an encephalitis was observed. In that case it was evident that the encephalitis did not progress from the surface. On the contrary, like an independent process it attacked predominantly the white matter of the hemispheres. The patient was a man, aged 47, who had a diffuse purulent cerebrospinal meningitis that involved especially the base of the brain. There was also a hemorrhagic encephalitis of the white matter of the hemispheres. Bacteriologic examination revealed *Bacillus coli*. Figure 14 gives a survey of the encephalitic process affecting the deep structures of the brain, namely, the white matter and the basal ganglia. Figure 15 shows the lesions in a myelin sheath picture, with patches of demyelinization around the blood vessels. This observation, that in such a case the encephalitic process does not progress from the surfaces but affects the substance of the brain in between the surfaces and is independent of the infection of the subarachnoid space and the ventricles, seems an important point.

The current opinion, to my mind erroneous, is that the infection travels from the meninges to the substance of the brain and that

encephalitis progresses with the greater intensity of the infection, or with its longer duration, deeper and deeper into the substance of the brain. Thus, Kaufmann mentioned the possibility of an encephalitis which travels from the meninges by way of the perivascular lymph spaces to the deeper parts of the brain, such as the basal ganglia. Encephalitic processes undoubtedly occur frequently in the substance of the brain adjoining the outer or inner surfaces of the brain. But such processes are directly responsible for a relatively insignificant part of the parenchymal lesions in purulent meningitis, when the widespread paled areas such as are demonstrated in this study are taken

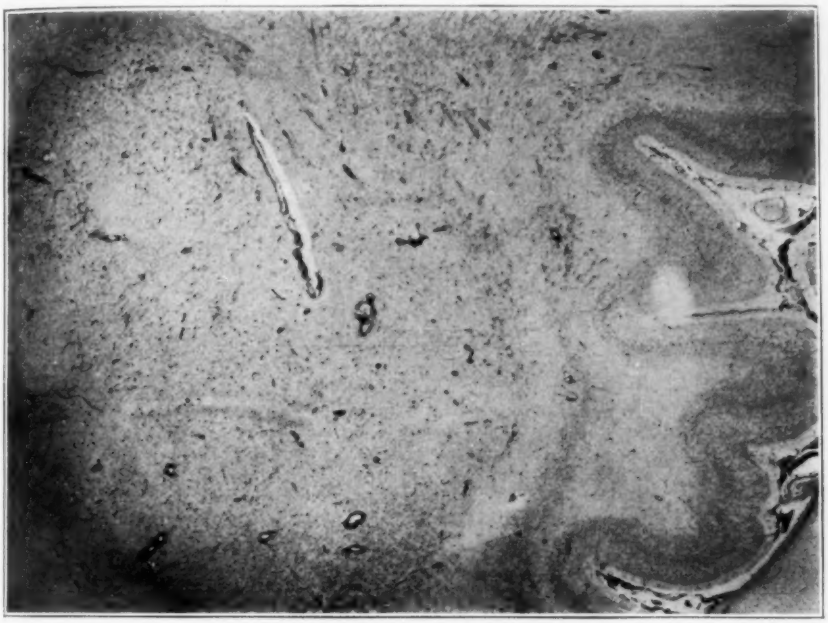


Fig. 14.—Meningitis plus encephalitis in a man, aged 47. *Bacillus coli* was found. Severe encephalitic changes in the whole subcortical area under the island of Reil. Meningeal infiltration in the cisterna of the fossa Sylvii. The cortex of the insula shows no encephalitic changes. This figure shows that the encephalitic process does not progress from the outer surface into the deeper parts of the substance of the brain. Nissl stain.

into account. When the blood vessels show leukocytic infiltrations and exudation into the surrounding tissues, only the cells in the immediate vicinity are damaged. The large areas where many cells have dropped out and the localized and diffuse palings are not caused in this way. If a fully fledged encephalitis intervenes, it is not merely an exaggeration or an intensification of the meningo-encephalitic process,

but it attacks the brain like a new process; it affects the deeper structures at the outset. My observations therefore confirm the experimental and clinical observations of Spatz [39] concerning the distribution of the encephalitic process. The deeper structures of the brain which lie in an intermediate zone between the inner and outer surfaces, that is, the basal ganglia, as a rule show no inflammatory changes in uncomplicated forms of meningeal infection. But from the observations in several cases of this study, marked and widespread necrobioses may occur in the intermediate zones, especially in the basal ganglia (figs. 3 and 4). No encephalitic process could be held responsible for these

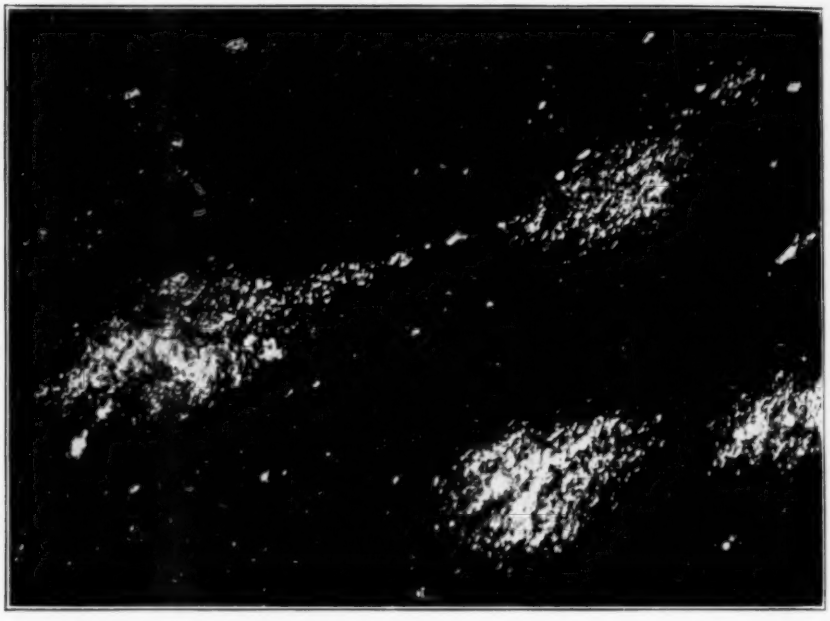


Fig. 15.—Type of patches of demyelinization occurring in a case of meningoencephalitis due to *Bacillus coli*. This type rarely occurs in uncomplicated purulent meningitis. Some of the patches are due to small hemorrhages (hemorrhagic encephalitis). Myelin sheath stain on unembedded material.

lesions. The explanation seems to be that such areas occurring in the depth of the substance of the brain have a relation to the vascular distribution.

39. Spatz, H.: Versuche zur Nutzbemachung der E. Goldman'schen Vitalfarbstoffversuche für Pathologie der Zentralnervensystem (die Trypanblau Meningitis), Allg. Ztschr. f. Psychiat. **80**:285, 1924; Das Lues cerebri- Paralyse-Problem und die pathogenetische Bedeutung des Ausbreitungsweges, Schweiz. Arch. f. Neurol. u. Psychiat. **16**:153, 1925; Encephalitis, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11.

There are various theoretical possibilities for an explanation of the pathogenesis of the lesions described. They might be of meningoencephalitic origin. They might be due to toxins of the infection. They might be specific parenchymal degenerations such as those that play such a controversial part in histopathologic literature in general; or they could be due to circulatory disorders. From this investigation it would appear that by far the largest part of cerebral lesions in purulent meningitis can be accounted for by a disturbance of the local circulation through the involvement of the blood vessels. The effect of toxins may also play a subsidiary rôle. That the blood vessels in the substance of the brain are involved in purulent meningitis, and even more so those in the meninges, has been demonstrated in this paper. The similarity of many of the paled areas found in purulent meningitis to the finer histologic appearance (ischemic cell change, etc.) of paled areas in which a vascular etiology has been sufficiently proved by pathologic and experimental investigations is striking. However, the effect of toxins should not be entirely overlooked. As to the origin of toxins, one has to consider not only the infection itself, but also the release of a large quantity of metabolic products by the necrosis of the cellular exudate in the meninges. It can be demonstrated that part of the leukocytic infiltration in the subarachnoid spaces, bordering the substance of the brain, is frequently necrotic early in the meningitic process (fig. 16). These toxins may affect directly the vessels and perhaps also to some extent the nervous parenchyma. The more circumscribed lesions of the nervous parenchyma are evidently to a large extent on a circulatory basis. For the more diffuse lesions, especially for the pathologic changes near the outer and ventricular surfaces, the toxic factor deserves more emphasis.

Stages of the Meningitic Process.—It is "almost impossible" to determine the age of histopathologic lesions, according to Müller,[41] who has carefully investigated this problem in especialy suitable cases. Nevertheless, an attempt to distinguish different stages in the development of cerebral lesions in purulent meningitis may be made. One deals here with an exceedingly complicated constellation of factors, which makes it difficult to compare cases with one another. But, in general, certain stages in the process of the disease may be tentatively indicated. A progressive reaction of the glia seems to belong to a very early phase. This was clearly demonstrable in one case. In the patient, a man, aged 38, a purulent meningitis developed following

40. Reference deleted by author.

41. Müller, G.: Zur Frage der Alterbestimmung histologischer Veränderungen im menschlichen Gehirn unter Berücksichtigung der örtlichen Verteilung, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:1, 1930.

otitis media. He died twenty minutes after admission to the hospital. The duration of the meningitic process was less than twenty-four hours. All through the cortex many mitoses of glia cells, in typical and also in regressive states, were found. In a single low power field, as many as ten mitoses were counted. In this stage, circumscribed proliferations of glia seem to occur more frequently than in later stages. The advanced changes in the nerve cells belong to a later stage. There may be diffuse clearings or more localized ones. These were observed mostly in the form of paled areas. (The state of damage that precedes these paled areas does not seem to be demonstrable with present methods.) Such palings can evidently develop into softenings with the proliferation of vessels, a later stage. This transition has been shown experimentally by Bodechtel and Müller.[42]

There may also be inflammatory reactions in the necrotic tissue. It is exceedingly difficult to make a statement with regard to the duration of these inflammatory stages. But it seems that definite abscesses belong to a late stage. In only one case of this investigation was a fully developed abscess observed, although in several others incipient ones were noted. That abscesses were so rarely found in these cases may be due partly to the fact that the whole process does not last long enough for their formation. Figure 16 shows a leukocytic patch that evidently signifies a beginning abscess. This picture shows various stages of necrosis. On the margin a proliferation of blood vessels can be observed. In this region the meninges are heavily infiltrated with leukocytes, macrophages and other basophilic round cells.

The formation of abscesses on the basis of a previous necrosis is of great pathologic significance. In meningitis, bacteria evidently may settle in a place where necrosis or softening exists, so that the formation of abscesses is secondary to the previous necrotic change which resulted from a circulatory disorder. It seems to me possible from these studies of purulent meningitis that the otogenic temporal abscess and other forms of abscess of the brain may in many cases be primarily not an infection, but a vessel-determined necrosis, on the basis of which, secondarily, infection and the formation of abscesses take place.

DIFFERENCES IN REACTION BETWEEN THE BRAIN OF A CHILD AND THAT OF AN ADULT IN PURULENT MENINGITIS

Differences in the reaction between the brain of a child and that of an adult to purulent meningitis are difficult to evaluate because so many heterogeneous factors have to be considered in each case: the

42. Bodechtel, G., and Müller, G.: Die geweblichen Veränderungen bei der experimentellen Gehirnembolie, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:754, 1920.

stage of the pathologic process, the topographic site of the process, the type of bacterial infection, the state of immunity, the type of treatment, etc. But undoubtedly differences do exist. In children the tendency to hydrocephalus is more pronounced; that is, hydrocephalus internus is found more often in children, and when it does occur it is more pronounced. The glial reaction in the first layer seems to be more pronounced in children, and there seems to be a more marked mobilization of microglia in the cortex. In the cerebellum the meningeal infiltration seems to penetrate more heavily between the lobules. The cerebellum of the child, however, seems to respond with less prolifera-

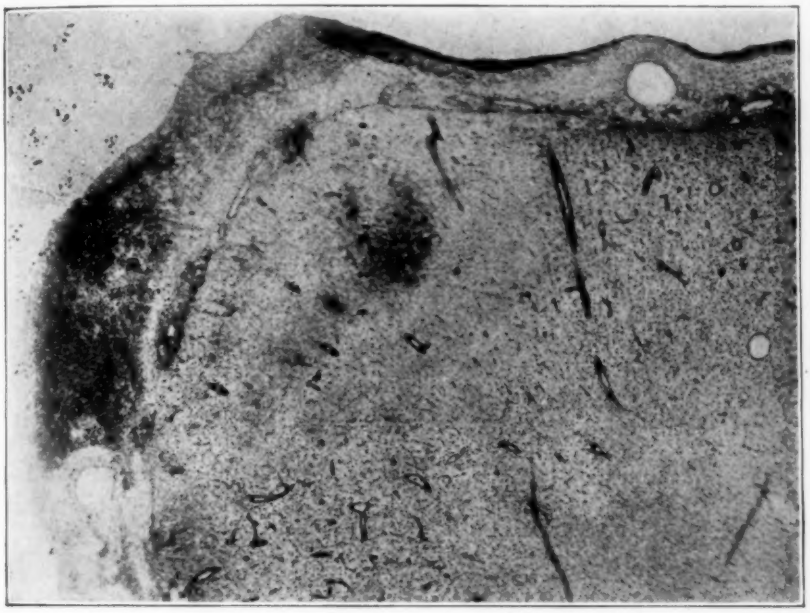


Fig. 16.—Area of the cortex showing various stages of necrosis. The leukocytic patch signifies the beginning of a purulent softening. On the margin of the paled area there is a proliferation of blood vessels. The meninges are heavily infiltrated, and part of the infiltrate has become necrotic. Nissl stain.

tion of the glia than that of the adult. The most important difference is the fact that apparently in children the deeper substance of the brain, especially the basal ganglia, is more frequently and more extensively affected by pale necroses. It also seems that the vessels are affected more extensively in the regions away from the inner and outer surfaces of the brain. These differences are stated as being only relative on account of the complexity of the factors entering into the pathologic picture of the individual case of purulent meningitis.

Clinical Significance.—The clinical significance of the cerebral lesions in purulent meningitis has still to be considered. To isolate cerebral symptoms clinically in the acute stage of the disease is extraordinarily difficult. I was impressed by the fact that in these cases the patients frequently present marked overactivity, and this symptom leads to their admission to psychiatric wards. This overactivity does not seem to be sufficiently noted in the description of the mental symptoms of meningitis in the literature.

As an example of the clinical significance of the lesions in the basal ganglia, which I have found especially in children, an important clinical observation of Foerster may be adduced.[43] In the course of an epidemic cerebrospinal meningitis in a boy, aged 5, severe general athetosis developed; later, this changed into a general rigidity and akinesis of the whole body. At autopsy a severe condition of the corpus striatum and pallidum was found, evidently determined by changes of the vessels due to the meningitic process.

Cases of recovery would have much importance for the clinical evaluation of the significance of the lesions here described. But clinical observations in cases in which recovery has occurred have to be considered with the greatest caution, for it is not always established beyond legitimate doubt that the cases in which the patients recovered were really purulent meningitis. Apparently both in children and in adults wrong diagnoses can be made easily. Haymann [44] has written a critical discussion of cases of otogenic meningitis with recovery published up to 1911.

Even though recovery from purulent meningitis occurs, the patient is left with residual neurologic and psychopathologic symptoms. The literature on this subject is far from satisfactory. The following are the main manifestations cited as sequelae: headaches, subjective sensations in the ears, paralyses and disorders of gait, disorders of vision, deafness, in young children deaf-mutism (Coester [45]), defects in intelligence (Coester), epilepsy (Ziehen), psychopathic deviations (Voisin and Paisseau [45]), aphasia (Semerád [46]), etc. Psychotic sequelae, which are often referred to, are not well documented in the literature (Sainton and Voisin [47]). Bourneville spoke of "meningitic idiocy."

---

43. Foerster, O.: Zur Analyse und Pathophysiologie der striären Bewegungsstörungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:1, 1921.

44. Haymann: Die Heilbarkeit der otogenen Meningitis, Zentralbl. f. Ohrenh. **9**:401, 1911.

45. Quoted by Bruns, Cramer and Ziehen (footnote 6).

46. Semerád, quoted by Oppenheim (footnote 19).

47. Sainton, P., and Voisin, R.: Les séquelles psychiques des méningites cérébro-spinales aiguës, Encéphale **1**:137, 1906.

It was formerly believed that all such symptoms were due to compression of the brain by the infectious exudate in the meninges. This theory was proved erroneous mainly through the work of French and Italian authors,[48] and a toxic etiology was assumed. In 1889, Oppenheim,[49] in drawing attention to neurologic sequelae of purulent meningitis, assumed that besides a chronic meningitis, the nature of which was a thickening and growing together of the meningeal membranes and the substance of the brain, focal encephalitic processes or small abscesses must play a part. In the present study it is suggested that the lesions of the nervous parenchyma that have been described here form the substratum of many of the cerebral symptoms that persist or appear in cases of purulent meningitis in which recovery occurs. The advantage of this explanation is that these lesions do not have to be assumed, but they can be demonstrated in practically every case. The function of the parts of the nervous parenchyma that show paled areas must be seriously impaired or abolished. It is most likely that such areas cannot be restored. Either they remain more or less in their original state for a long time or they lead to various forms of secondary inflammation and softening. These severe and often widespread conditions of the nervous parenchyma, which may involve any part of the central nervous system, are evidently the cause of the cerebral symptoms observed in patients who have recovered from the acute disease. Next in importance is the often persistent hydrocephalus and a general disturbance in the circulation of the cerebrospinal fluid. Further investigation of the mild forms of hydrocephalus that follow purulent meningitis [50] should be undertaken. Changes due to encephalitic influences seem to take third place. I am therefore in disagreement with the prevalent view, as expressed by Southard;[51] namely, that "it is rare to find in acute leptomeningitis any single lesion which is necessarily incurable." On the contrary, the observations of this study show that even very early in the purulent meningitic process, damage may be done to the parenchyma of the central nervous system which cannot be completely restored.

Purulent meningitis is one of the most fatal diseases known; but it is not yet clear what actually causes death in this condition. A general infection of the blood has been assumed (Davis [52]). It is

48. Padoa, G.: Contribution à l'étude des séquelles éloignées des méningites, Encéphale **5**:540, 1910.

49. Oppenheim, H.: Ueber ein bei Krankheitsprozessen in der hinteren Schädelgrube beobachtetes Symptom, Neurol. Zentralbl. **8**:132, 1889.

50. Compare the interesting study by Cornelia de Lange (Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:433, 1929).

51. Southard (footnote 11, second reference).

52. Quoted by Körner and Grünberg (footnote 9).

also believed that toxins affect the whole organism, or merely the brain alone. Ruttin [52] saw paralysis of the vagus as the cause of death in a case of "circumscribed meningitis." According to Buzzard and Greenfield, the meningeal inflammation causes a rise in intracranial pressure and thereby "the blood supply to the brain is diminished and the vital centers, already poisoned by bacterial poisons, are deprived of nutrition." It seems that the lesions described, independent of the mechanical factor of the rise of intracranial pressure, may have something to do with certain forms of death in meningitis.

I believe that from these pathologico-anatomic observations therapeutic suggestions can also be derived. If it is true that the vast majority of the cerebral lesions in purulent meningitis are due to circulatory factors, then therapeutic procedures directed toward relief of the circulatory system in purulent meningitis may deserve more attention than has been bestowed on them so far.

SUMMARY

1. Apart from the encephalitic and toxic-degenerative changes hitherto described in the literature, other extensive lesions of the nervous parenchyma occur in purulent meningitis.

2. It is chiefly the cortex that is involved; but the subcortical structures, such as the basal ganglia, may also be severely affected, especially in children.

3. Most of the lesions are on a circulatory basis, with toxic factors probably playing a subordinate part. They are not due to encephalitic changes. If a fully fledged encephalitis supervenes, the infection does not progress from the outer and ventricular surfaces, but the encephalitis attacks the central parts of the substance of the brain like an independent process (fig. 14).

4. Histologic details are discussed on the basis of an examination of twenty-four cases.

FRACTURE OF THE SKULL WITH INJURY OF THE BRAIN

THE DIAGNOSIS OF LACERATION OF THE ORBITAL SURFACE OF THE FRONTAL LOBES *

E. S. GURDJIAN, M.D.
AND
N. H. SCHLAFER, M.D.
DETROIT

Cerebral localization in cases of injury of the brain is frequently difficult. It is common to find postmortem changes in the brain that were little suspected from the clinical examination. Large hemorrhages and extensive lacerations in otherwise active parts of the brain may cause no more than complete unconsciousness. Hemianopia, sensory changes, olfactory manifestations and difficulties in hearing may not be brought to light in acute cases of craniocerebral injury because of lack of cooperation by the patient. The motor system is practically the only one that gives definite data on localization. Destruction of the motor cortex and the pyramidal tracts is invariably associated with alterations of the reflexes and motor ability. A certain number of cases with motor dysfunction show jacksonian epilepsy. This is usually the result of destructive changes in the motor system, although it may be the expression of increased intracranial pressure.

At the Receiving Hospital, Detroit, where hundreds of examples of fracture of the skull are seen every year, we have been impressed by the large number of cases with laceration of the orbital surface of the frontal lobe seen at autopsy. Of thirty-one consecutive postmortem cases, seven presented lacerations in this location. A careful study of these patients before and after death has led us to believe that such cases can frequently be diagnosed clinically if certain conditions are observed.

It should be emphasized that in cases of fracture of the skull with injury of the brain there are forces that damage the brain by pressure of bony parts against it (direct or contrecoup) or possibly by pushing the cerebral substance against bony parts (Peet [1]). Therefore, lesions of this type are different in extent from those produced by a knife, a small tumor or a bullet. In craniocerebral injuries there is massive damage to the brain, dependent on the position of soft parts in relation to bony portions, so that such injury may rightly be termed "regional in type."

* Submitted for publication, Jan. 13, 1931.

1. Peet, M. M.: Symptoms, Diagnosis and Treatment of Acute Cranial and Intracranial Injuries, Industrial Doctor, vol. 5, no. 7, 1927.

Because of its position in relation to the frontal and sphenoidal bones, the orbital surface of the frontal lobes is frequently damaged en masse, the sharp edge of the lesser wing of the sphenoid causing an added injury to the tip of the temporal lobe. Such lesions of the frontal lobe are usually the result of distant forces which push the brain against the orbital surface of the frontal and sphenoidal bones (occipital and vertex frontal fractures). Occasionally such lesions may be the result of direct forces (frontal fractures passing through the anterior fossa).

In the case of a lesion of the orbital surface of the frontal lobes there is involvement of an essentially silent part of the brain, with the exception of the region of the lower end of the sylvian fissure and its junction with the inferior extreme of the fissure of Rolando. This part is the intermediate cortical motor center, and a portion of the face center extends into it (Campbell [2]). On the left side it has the added function of motor speech. When there is an injury to the orbital surface of the frontal lobe extending far enough posterolaterally to include the lower end of the motor center, with resultant irritative phenomena, the only manifestation of this nature would be jacksonian epilepsy or paralysis of the face on the opposite side and, if the lesion is extensive enough, a possible paresis of the contralateral upper limb.

When, therefore, a patient shows irritative motor phenomena, a diagnosis of injury and laceration of the orbital surface of the frontal lobes can be made. Observations with the x-rays, the position of the fracture and the state of consciousness of the patient are added helps in recognizing the condition. In cases of fracture of the skull it is safe to assume that a lesion causing jacksonian epilepsy of the face, the patient being completely unconscious, is of much greater extent than the cortical motor center of the face; that it probably involves the orbital surface of the frontal lobe, extending far enough posteriorly to include the facial center. Localized depressed fractures overlying the motor regions may form an exception to this generalization. This assumption is illustrated by the following cases.

REPORT OF CASES

CASE 1.—*Circumoral twitching following a fracture of the skull with injury of the brain. Occasional twitching of the upper limbs. Autopsy showed laceration of the orbital surface of both frontal lobes.*

L. S., a man, aged 20, entered the Receiving Hospital in an unconscious state after an automobile accident. He was very restless and vomited several times.

Examination revealed a large hematoma in the left parieto-occipital region with no laceration. The ocular fundi were normal. There were no evident palsies

2. Campbell, A. W.: Histological Studies of Localization of Cerebral Function, London, Cambridge University Press, 1905.

of the cranial nerves. The thorax and abdomen were apparently normal. The blood pressure was 110 systolic and 90 diastolic.

The course in the hospital was characterized by a gradual rise in temperature to 107 F. before death, which occurred seventy hours after admission to the hospital. For thirty-six hours before death there was marked twitching about the mouth on both sides and occasional twitching of the upper limbs. The reflexes remained the same throughout, except for a questionable Babinski sign on the right side toward the last. The patient did not regain consciousness.

Autopsy revealed a fracture 8 inches (20.32 cm.) long, extending from the frontal protuberance posteriorly for 3 inches (7.6 cm.), then toward and involving the posterior third of the sagittal suture. The dura was edematous. The sinuses were normal. The brain was congested throughout. The orbital surfaces of both frontal lobes were lacerated, the softening extending as far back as the sylvian fissure laterally and the temporal pole medially.

Comment.—In this case there was jacksonian epilepsy of the face, with occasional involvement of the upper limbs. The pathologic observations showed laceration of the orbital surface of both frontal lobes, including injury to the cortex surrounding the lower end of the sylvian fissure. The lesion of the frontal lobes was a contrecoup effect.

CASE 2.—*Twitching about the mouth for one day before death and occasional twitching of the right upper limb following a fracture of the skull with injury of the brain. Autopsy showed laceration of the orbital surface of both frontal lobes, fractured ribs, ruptured spleen and retroperitoneal hemorrhages.*

T. B., a man, aged 45, entered the hospital after an automobile accident. He was very restless and noisy, and was disoriented at the time of the first visit.

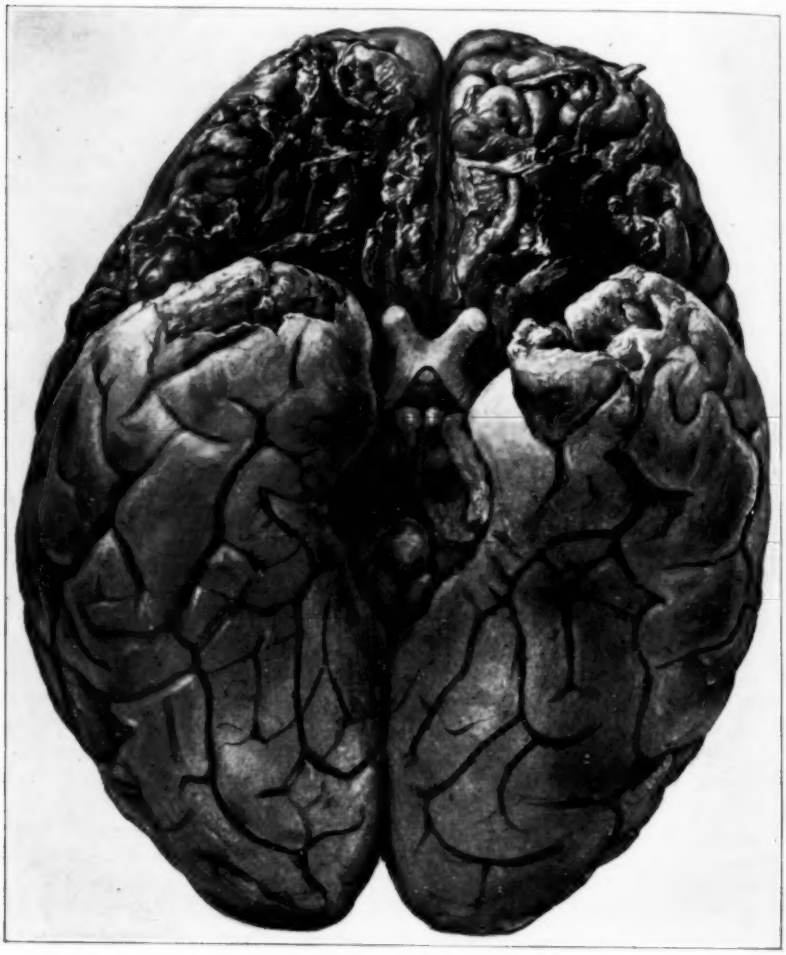
Examination revealed multiple lacerations and abrasions of the scalp and face. A laceration near the external occipital protuberance was deep. The right pupil was slightly larger than the left; both pupils reacted to light. The ocular fundi were normal. There was no bleeding from the ears or nose. There was evidence of fractured ribs. The abdomen was slightly tender throughout. The reflexes were present, and there was a questionable Babinski sign on the left. The spinal fluid was uniformly bloody. The blood pressure was 150 systolic and 70 diastolic. A roentgenogram showed an occipital fracture.

The course in the hospital was characterized by a gradual increase in the severity of the symptoms. The patient had several attacks of twitching about the mouth and twitching of the right arm. He was in the hospital for sixty-one hours. The temperature became progressively elevated, until it was 104 F. before death. The reflexes remained about the same throughout the course.

Autopsy revealed a fracture extending from the internal occipital protuberance to the jugular foramen on the left. The brain was generally edematous and wet. There was blood in the subarachnoid space. The orbital surface of both frontal lobes was markedly lacerated. The laceration extended as far as and involved somewhat the temporal lobes. There were several fractured ribs; the spleen also was ruptured.

Comment.—Case 2 is also an example of jacksonian epilepsy of the face due to laceration and destruction of the orbital surface of the frontal lobes. Here, again, the frontal lesion was caused by a force applied at the occipital pole of the skull, with pushing of the

brain against the orbital part of the frontal and sphenoidal bones. In this case, there was an occipital fracture causing motor symptoms of an irritative nature, which probably caused frontal lacerations by contrecoup.



Lacerations of the orbital surface of the frontal lobes in case 3. There is more involvement of the right side on which it extends posterolaterally to involve the region of the lower end of the sylvian fissure. In this case there was jacksonian epilepsy of the tongue and face.

CASE 3.—*Jacksonian epilepsy of the left side of the face and tongue, and occasional involvement of the left upper extremity before death. Autopsy showed laceration of the orbital surface of the right frontal lobe and a slight involvement of the left.*

G. P., a man, aged 44, entered the hospital in a semicomatose condition following a fall. He was practically disoriented as to time and space.

Examination revealed a contusion over the right parietal region. The pupils were equal and regular, but reacted sluggishly to light. The ocular fundi were normal. There were convulsive seizures of the tongue, clonic in type. At each to and fro movement the tongue deviated to the left. Associated with this there were also circumoral twitchings and occasional twitchings about the left eye. The abdominal skin reflexes were abolished. A Babinski sign was present bilaterally, and it was noted that the patient used the left upper limb less than the right. Roentgen examination revealed a fracture in the right parietal region extending from the pituitary fossa to the lambdoid sutures. A diagnosis of laceration of the orbital surface of the frontal lobe with possible cortical hemorrhages over this area was made.

The course in the hospital was characterized by an accentuation of the jacksonian seizures. A right subtemporal decompression operation was performed. On opening the dura a few clots were removed; the underlying brain was red and definitely contused. The patient's condition did not improve, and he died at the end of eight days, having had generalized convulsions toward the last. Hypertonic solutions were administered intravenously, and lumbar punctures were also performed. The temperature rose to 108 F. before death.

Autopsy revealed a clean operative wound, with little herniation of the brain at its site. The meninges were red and edematous. There was blood in the subarachnoid space, particularly over the right hemisphere. There were a few clots in the temporosphenoidal region and the anterior fossa on the right side. There was marked laceration of the orbital surface of the right frontal lobe with a definite contusion of the cortex surrounding the lower end of the sylvian fissure. A fracture, 5 inches (12.7 cm.) long, extended from the right temporoparietal region toward the occipital and crossed the midline just past the squamous portion of the occipital. Microscopic studies of the motor cortex showed several hemorrhages. The sections from the lower end of the medulla did not show any peculiar involvement of the hypoglossal nuclei.

Comment.—This case probably represents one of the few cases of jacksonian epilepsy of the tongue that have been reported in the literature. The diagnosis of laceration of the frontal lobe involving also the lower end of the sylvian fissure was made clinically and proved by autopsy.

CASE 4.—*Depressed fracture of the left frontoparietal region. Jacksonian epilepsy of the face and upper limb on the right. Autopsy showed laceration of the orbital surface of the left frontal lobe.*

S. S., a boy, aged 3, entered the hospital in an unconscious state after an automobile accident.

Examination revealed an abrasion in the left frontoparietal region with a palpable depression. The left pupil was constricted. Examination of the ocular fundi was impossible. There was a questionable right facial weakness of cortical type. The left upper limb was definitely spastic, with catatonic rigidity. Lumbar puncture elicited bloody spinal fluid. There was a bilateral Babinski sign. Two or three hours after entrance to the hospital, convulsive seizures developed involving the right side of the face and occasionally the right upper extremity.

The course in the hospital was characterized by an accentuation of the signs and symptoms. About three hours after admission, an operation was performed for elevation of the depression and removal of blood clots. The dura was red and inflamed. The brain was contused in several places at the site of depression. The patient was in the hospital for thirty-eight hours.

Autopsy revealed extreme edema of the brain with a certain amount of flattening of the convolutions. There were no areas of subarachnoid hemorrhage or clots. There was a marked laceration of the orbital surface of the left frontal lobe. A fracture line extended from the left frontoparietal region into the superior aspect of the orbit, ending at the margin of the superior orbital fissure.

Comment.—In this case again there was jacksonian epilepsy of the face and upper limb on the right, which eventuated in generalized convulsive seizures before death. The generalized convulsions were probably an expression of a traumatic encephalitis and increased intracranial pressure, but the first jacksonian manifestations were diagnostic of the lesion, namely, an orbital frontal laceration involving the face and the motor centers for the upper limbs.

As has already been stated, the orbital surface of the frontal lobe is essentially a silent region, with the exception of the region of the lower end of the sylvian fissure. Anatomically, it is possible that only the silent region may be destroyed in a fracture of the skull with injury of the brain; it is possible also that a laceration in the motor area may not be sufficiently serious to cause irritative or paralytic phenomena. Cases 5 and 6 belong to a group in which no irritative phenomena occurred. In both, autopsies revealed involvement of the lower end of the sylvian fissure; yet, this was not associated with irritative phenomena. However, the clinical observations in these cases would have suggested the possibility of lacerations of the orbital surface of the frontal lobes.

CASE 5.—*Marked laceration of the orbital surface of the frontal lobes. No jacksonian epilepsy. Death after four and one-half hours in the hospital. Autopsy.*

F. F., a man, aged 29, entered the hospital in an unconscious state after an automobile accident. He was stuporous.

No notes are available relative to the course in the hospital, except that he suddenly became cyanotic, the pulse became weak, and he died.

Autopsy revealed an edematous brain. The sinuses were normal. There were several clots in the anterior fossae on both sides. There was marked laceration of the orbital surface of both frontal lobes, which involved the temporal pole on both sides. There was a fracture, 6 inches (15.24 cm.) in length, extending from the region of the parietal bone in the midline to the left jugular foramen.

Comment.—This case is an example of laceration of the orbital surface of the frontal lobes with no associated motor symptoms. If the patient had lived long enough, and if roentgen examinations had shown the fracture, the presence of such lacerations might have been suspected. Evidently, in this case the frontal lacerations were due to contrecoup. This case of injury to the motor cortex did not show jacksonian epilepsy.

CASE 6.—*No jacksonian epilepsy. Complete unconsciousness. Autopsy showed laceration of the orbital surface of the left frontal lobe, with a slight laceration on the opposite side.*

J. D., aged 88, entered the hospital in an unconscious state after an automobile accident. There were extensive lacerations of the scalp in the left parietal region. The pupils were equal and reacted to light. The ocular fundi were normal. There were no evident palsies of the cranial nerves. The thorax and the abdomen were normal. The blood pressure was 135 systolic and 60 diastolic. The reflexes were not increased.

The course in the hospital was characterized by occasional lucid periods. The blood pressure remained about the same throughout. No epileptic fits were noted. The patient was in the hospital for thirty-seven hours before death.

Autopsy revealed a fracture, 1½ inches (2.66 cm.) in length, of the left frontal bone, beginning at the supra-orbital foramen and extending upward and posteriorly. There was a laceration of the orbital surface of the left frontal lobe involving the entire surface and a slight softening on the opposite side.

Comment.—This case is closely similar to case 5 in that the laceration involving the region of the lower end of the sylvian fissure did not cause jacksonian epilepsy.

Case 7 illustrates the fact that irritative motor phenomena of the face may be an expression of generalized convulsive seizures, which are seen frequently in cases of fracture of the skull with injury of the brain, particularly in children. Such seizures may be the result of increased intracranial pressure with associated traumatic encephalitis. They can usually be distinguished from the jacksonian type of seizures. However, it should be mentioned that attacks which begin as jacksonian and are definitely localized may in time become generalized and simulate the picture to be depicted in case 7.

CASE 7.—*Fracture of the skull with generalized convulsive seizures. Extensor spasm of the entire body. Occasional twitching about the left side of the face. Autopsy showed laceration of the orbital surface of the frontal lobes.*

N. F., a boy, aged 10, entered the hospital in an unconscious state after an automobile accident. It was noted that he went into extensor spasms frequently, with frothing at the mouth. There was a questionable right facial weakness. Convulsive seizures occurred as often as every two minutes. An occasional twitching was noted also about the left side of the face. There was generalized spasticity of the entire body. The blood pressure was 178 systolic and 104 diastolic; one-half hour later it was 150 systolic and 100 diastolic. Spinal puncture yielded free blood in the spinal fluid. There were bilateral patellar clonus and Babinski sign. The reflexes were increased in both the upper and the lower extremities.

A right subtemporal decompression was performed. There was much herniation at the site of the operation and a 50 per cent solution of dextrose was administered to control the intracranial pressure. The brain appeared fairly normal, except for marked flattening of the convolutions. The patient was in the hospital for nine hours. At the time of the operation it was not thought advisable to explore the opposite side because of the poor condition of the patient.

Autopsy revealed an occipital fracture extending into the jugular foramen on the right and another line at an acute angle extending toward the right ear. There was a slight laceration of the orbital surface of the frontal lobe on the left side, with some laceration of the right lateral surface of the hemisphere in the region of the motor cortex. A marked increase in the intracranial pressure was evidenced by flattening of the cortex.

GENERAL COMMENT

Fracture of the skull with injury of the brain is an important neurosurgical problem. Much has been reported on the subject, and a review is beyond the purposes of this paper. It is of interest, however, that Foix,[3] Peet,[1] Naffziger,[4] McClure and Crawford,[5] Rand[6] and others have brought out the fact that in occasional cases of craniocerebral injury the pathologic changes found at operation or autopsy may not support the clinical conclusions. This must have been the experience of many investigators. However, in the majority of cases pathologic changes are found that are responsible directly for the antemortem observations. Lack of macroscopic and even of microscopic evidence does not necessarily rule out intracellular changes due to concussion, toxic causes and similar factors. One important point is that blood in the ventricular and subarachnoid spaces, with its irritating influence on the motor system, may alter the clinical picture.

As early as 1878, Duret[7] emphasized the prevalence of lacerations of the frontal lobe in cases of fracture of the skull. LeCount and Apfelbach,[8] in an excellent report on 504 cases of craniocerebral injury observed post mortem, stated that in 178 the fracture involved the posterior fossa; in 166 it occurred in the middle fossa, and in 61 in the anterior fossa. There were 49 fractures of the vault. Approximately 89 per cent of the fractures of the posterior fossa showed associated involvement of the frontal lobes. The orbital surfaces of the frontal lobes were injured most frequently. In fractures of the middle fossa, 70 per cent were associated with bruises and lacerations of the outer margins and the orbital surfaces of the frontal lobes.

3. Foix, C., in Nelson: Loose-Leaf Medicine, New York, T. Nelson & Sons, 1920, vol. 6, p. 137.

4. Naffziger, H. C., in Nelson: Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1927, vol. 3, p. 833.

5. McClure, R. D., and Crawford, A. S.: The Management of Craniocerebral Injuries, Arch. Surg. **16**:451 (Feb.) 1928.

6. Rand, C. W.: The Significance of a Dilated Pupil of a Homolateral Hemiplegic Side in Cases of Intracranial Hemorrhage Following Head Injuries, Arch. Surg. **18**:1176 (April) 1929.

7. Duret, H.: Études expérimentelles et cliniques sur les traumatismes cérébraux, Paris, 1878.

8. LeCount, E. R., and Apfelbach, C. W.: Pathologic Anatomy of Traumatic Fractures of Cranial Bones, J. A. M. A. **74**:501 (Feb. 21) 1920.

In fractures of the anterior fossa, the injury to the frontal lobes was direct in 57 per cent of the cases. The work of these investigators emphasizes the importance of contrecoup injury in the mechanism of production of these lesions. In 1929, Martland and Beling [9] reported 309 autopsies with 82 per cent of lacerations and associated hemorrhage. In their series, contrecoup injuries constituted 57 per cent of the total group. With such a large percentage of contrecoup lesions, the importance and prevalence of regional and massive damage becomes apparent. Of the cases reported here, all but one showed injury to the frontal lobes by contrecoup. The conclusions of LeCount and Apfelbach emphasize the frequency of injury of the frontal lobe, and in particular of the orbital convolutions.

According to Foix,[3] lesions of the frontal lobe are characterized by torpor, mild inequality of tendon reflexes and disorders of speech. This is not necessarily pathognomonic of lesions of the frontal lobe, as Foix agrees. Our studies lead us to believe that orbital lacerations of the frontal lobe may be diagnosed clinically. With a patient completely unconscious and a fracture of the posterior fossa or of the vault, and with signs of motor irritation or paralysis, particularly if they involve the face and possibly also the upper limbs, one may with fair surety make a diagnosis of laceration of the orbital surface of the frontal lobes. In the group reported here, such a diagnosis could have been made in more than 50 per cent of the cases. This diagnosis could have been arrived at also in a case reported by Sharpe: [10]

> Daniel entered the hospital in an unconscious state. There was an occipital laceration with an underlying fracture. The right pupil was smaller, the right knee jerk was more active and there was a bilateral Babinski sign. The cerebrospinal fluid was bloody. Twelve hours after admission, the patient had an attack of jacksonion epilepsy involving the right arm and extending to the face and leg. Autopsy revealed an occipital fracture extending from the external occipital protuberance to the foramen magnum, and then anteriorly through the basilar process. There were extensive lacerations of the orbital surfaces of both frontal lobes.

Unfortunately, irritative phenomena are rare. In our series of over 3,000 cases, to be reported later, jacksonian epilepsy was observed in only 5-6 per cent. Sharp found 27 instances in 487 cases. We think that in the absence of irritative motor signs, paralytic motor phenomena should be sought. The latter would have the same clinical significance. Cortical facial paralysis and inequality of tendon reflexes in the upper limbs may have the same diagnostic import as irritative manifestations. Generalized seizures due to increased intra-

9. Martland, H. S., and Beling, C. C.: Traumatic Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **22**:1001 (Nov.) 1929.

10. Sharpe, W.: Brain Injuries, Philadelphia, J. B. Lippincott and Company, 1920.

cranial pressure and traumatic encephalitis do occur; we purposely included such a case in our report. Such cases usually can be distinguished from those with jacksonian attacks. However, Peet [1] asserted that even localized motor manifestations may be caused by localized pressure changes in the brain. It is important to mention that jacksonian attacks may become generalized toward the last, probably owing to increasing intracranial pressure and traumatic encephalitis.

Extensive lacerations of the orbital surfaces of the frontal lobes must be of grave prognostic import. The cases reported by LeCount and Apfelbach testify to this. It would be of interest to know whether extensive adhesions involving the orbital frontal convolutions exist in fatal chronic cases of fracture of the skull. However, we have seen several patients with jacksonian epilepsy of the face due to fracture of the skull recover.

SUMMARY

1. Laceration of the orbital surface of the frontal lobes is common in cases of fracture of the skull with injury of the brain.

2. Owing to the anatomic relations of the anterior fossa, the lateral inferior aspect of the hemisphere, at the junction of the anterior and the middle fossae, is also seriously damaged in such cases.

3. Extreme stupor, jacksonian epilepsy or paralytic changes of the face and possibly the upper limb, fracture in the posterior fossa, the vault or passing through the anterior fossa (in the absence of localized depressions) and bloody spinal fluid were characteristic of fully 50 per cent of the cases of laceration of the inferior aspect of the frontal lobe.

4. Such lacerations are fatal in the majority of the cases.

BASOPHILIC ADENOMA OF THE HYPOPHYSIS WITH ASSOCIATED PLURIGLANDULAR SYNDROME

REPORT OF A CASE *

HAROLD M. TEEL, M.D.
CLEVELAND

The profound influence of the anterior lobe of the hypophysis on the other endocrine organs, and particularly on the gonads, has been clearly demonstrated during the past few years by numerous experimenters; notably by Smith and his collaborators,[1] Evans and his co-workers,[2] Zondek [3] and Aschheim.[4] It has been shown that precocious sexual maturity may be induced in immature animals (rats, mice, dogs and monkeys) of both sexes, both by means of frequently renewed transplants of fresh tissue from the anterior lobe and by the administration of extracts prepared from this tissue. This effect is much more rapid and striking in the case of the female; indeed, sucklings may be brought to maturity in from two to four days, as evidenced by great hypertrophy and hyperemia of the uterus; opening of the vagina, with vaginal cellular content characteristic of the estrum, and marked hypertrophy of the ovaries, with follicular ripening, ovulation and the subsequent formation of corpora lutea. In adult females

* Submitted for publication, Feb. 16, 1931.

* From the Department of Surgery, the Lakeside Hospital.

1. Smith, P. E., and Engle, E. T.: Experimental Evidence Regarding Rôle of Anterior Pituitary in Development and Regulation of Genital System, Am. J. Anat. **40**:159 (Nov.) 1927.

2. Evans, H. M.: The Function of the Anterior Hypophysis, Harvey Lectures, Philadelphia, J. B. Lippincott Company, 1924. Evans, H. M., and Simpson, M. E.: Comparison of Anterior Hypophyseal Implants from Normal and Gonadectomized Animals with Reference to Their Capacity to Stimulate Immature Ovary, Am. J. Physiol. **89**:371 (July) 1929; Sex Difference in Hormone Content of Anterior Hypophysis of Rat, ibid., p. 375; Effect of Pregnancy on Anterior Hypophysis of Rat and Cow as Judged by Capacity of Implants to Produce Precocious Maturity, ibid., p. 379; Comparison of Ovarian Changes Produced in Immature Animals by Implants of Hypophyseal Tissue and Hormone from Urine of Pregnant Women, ibid., p. 381.

3. Zondek, B.: Ueber die Funktion des Ovariums, Ztschr. f. Geburtsh. u. Gynäk. **90**:372, 1926.

4. Aschheim, S.: Ueber die Funktion des Ovariums, Ztschr. f. Geburtsh. u. Gynäk. **90**:387, 1926.

the same treatment results in superovulation and a great increase in the size of the ovaries. In rats, prolonged treatment often gives rise to follicular cysts.

In addition to its gonad-stimulating properties, anterior hypophyseal tissue has been shown to have a considerable influence on some of the other endocrine organs. If transplants of this tissue are made daily over a period of weeks or months, a considerable enlargement of the adrenal cortex and thyroid is produced.

Experimental evidence indicates that the substance or hormone responsible for the gonad-stimulating effect is elaborated in the basophilic cells of the anterior lobe. That the principle that effects the hypertrophic changes in the gonads is also responsible for the hypertrophic change in the other endocrine organs would appear not unlikely.

Earlier experimental and pathologic studies demonstrated that the eosinophilic cells of the anterior lobe secrete a hormone that promotes both normal growth and pathologic overgrowth. Thus, in a large number of cases studied by Cushing and his co-workers, gigantism and acromegalia were invariably associated with an eosinophilic adenoma of the hypophysis.

Unlike the adenomas of the eosinophilic and chromophobe cells, basophilic adenoma of the hypophysis is a decidedly rare lesion. Further, while several cases of basophilic adenoma have been reported, I have not encountered in the literature a case in which coincident hypertrophic changes have been found in the gonads and other endocrine glands.

The following case is presented in which basophilic adenoma of the hypophysis was found associated with enlargement of the ovaries, the suprarenal cortex and the thyroid, an uninvoluted thymus, as well as an unusual number of islets in sections taken at random from the pancreas.

REPORT OF CASE

History.—H. E. D., a single, white woman, aged 20, was admitted to the service of Dr. F. S. Gibson at the Lakeside Hospital on Nov. 3, 1929, because of chills, fever and vomiting of two days' duration. The onset was abrupt; the day before admission the patient complained of pain in the neck. On the day of admission she became unconscious and several mild convulsions occurred. The family history was irrelevant. The patient had had the usual diseases of childhood, otitis media at 6 and jaundice at 7 years of age. At the age of 9, she began to "menstruate," and the flow was continuous for four months. There was no further bleeding until the onset of an apparently normal puberty at the age of 14. Menstruation had always been irregular, the interval varying from five weeks to five months. During the year preceding admission, the periods were fairly regular at five weeks, the flow moderate in amount and the duration five days. At the time of admission the menstrual period was two weeks overdue.

For the previous five years the patient had been troubled by dyspnea on exertion and a sense of precordial oppression. During this period there was a progressive gain in weight until a maximum of 206 pounds (93.4 Kg.) was reached

seven months before admission to the hosptial. Fifteen months before admission, because of excessive fatigue and obesity, she consulted her local physician who noted marked hirsutism and found that the basal metabolic rate was +33. A diagnosis of "pituitary infection" was made, and the patient was given some sort of pituitary extract by mouth, which was continued for eight months. At that time the basal metabolic rate was found to be + 42. Deep roentgen therapy was administered to the thyroid every week for four months. The basal metabolic rate was not subsequently estimated, but the pulse rate was said to have dropped from 125 to 85. A few weeks before admission, the patient stated that her health was better than it had been for three years. During the past seven months she had lost 28 pounds (12.7 Kg.) through dieting.

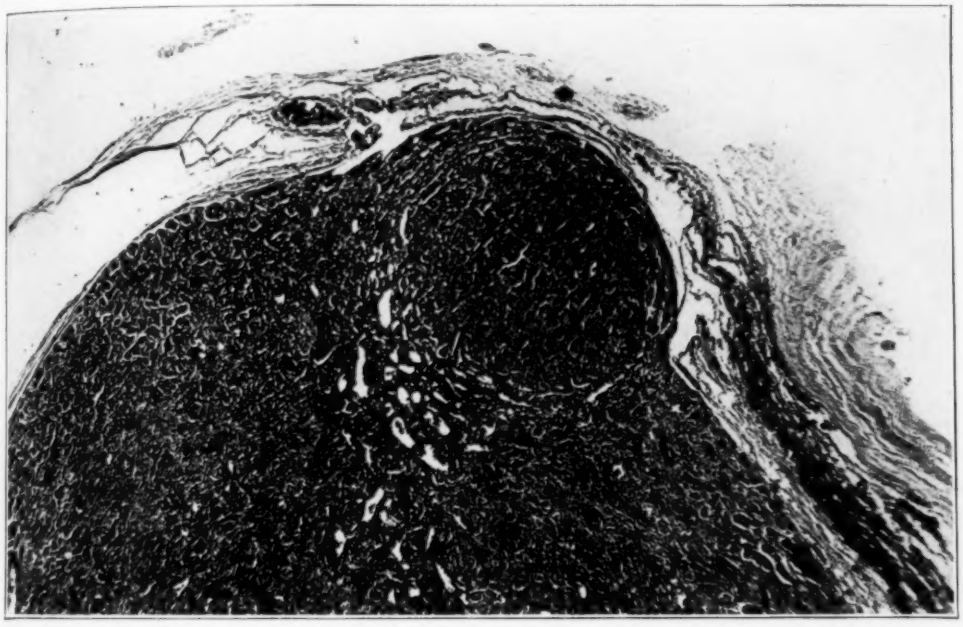


Fig. 1.—Photomicrograph, low power, showing the hypophyseal basophilic adenoma.

Physical Examination.—Physical examination revealed an irrational, obese, white woman tossing about in bed. The unconsciousness, interrupted by occasional generalized convulsive seizures, made a routine physical examination impossible. The skin was pale, fine, moist and not pigmented. The face was covered with a heavy black beard, which had obviously been subjected to constant shaving for some time. The thorax, abdomen and extremities were covered with coarse black hair. The thyroid gland was symmetrically enlarged and of a rather firm consistency perhaps owing to roentgen treatments. The physical signs of meningitis, including stiff neck and Kernig's and Brudzinski's signs, were present. On admission the temperature was 38.5 C. (101.3 F.). Lumbar puncture performed on admission revealed a turbid fluid under increased pressure, with 14,000 leukocytes per cubic millimeter.

Course.—In spite of supportive treatment with repeated clysis and intrathecal injections of antimeningococcus serum, the patient grew progressively worse and died on the fourth day with a terminal elevation of temperature to 42.3 C. (108.1 F.). During the hospital course, intracellular and extracellular diplococci were found in the spinal fluid, although cultures from the blood and the spinal fluid did not show growth. However, meningococci were cultivated from cisternal puncture performed at autopsy. Unfortunately, the patient came from out of town in a comatose state, and the history as regards the endocrine disturbance is lamentably incomplete, having been obtained through a relative.

Necropsy.—Autopsy was performed on the day of the patient's death, and pathologic examination revealed a suppurative meningococcic leptomeningitis as

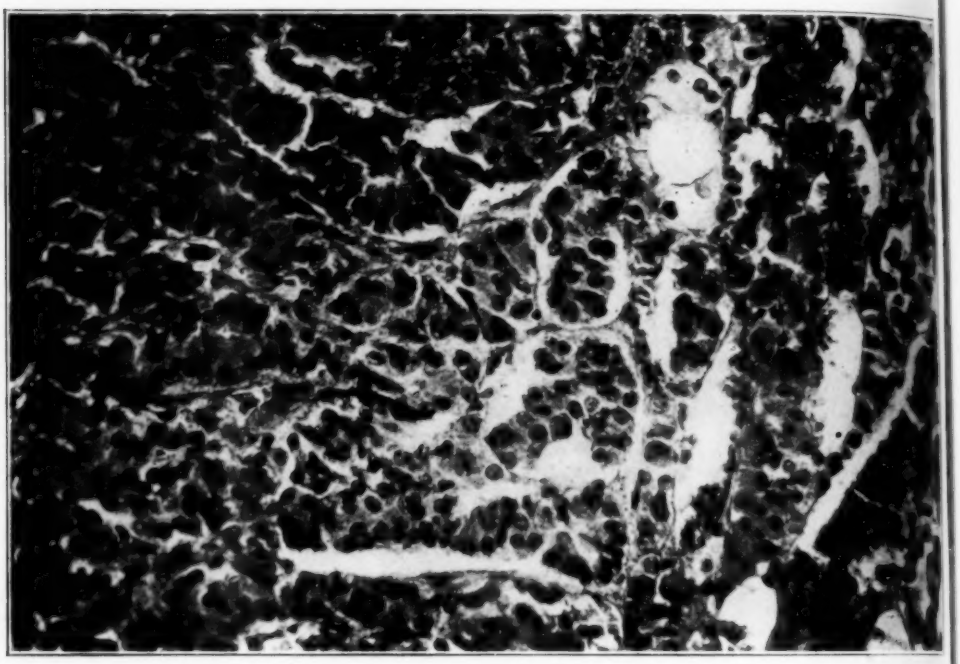


Fig. 2.—Portion of the section through the adenoma shown in figure 1, under greater magnification.

the cause of death. My interest, however, is centered about the condition in the endocrine organs, a description of which follows:

Hypophysis: Grossly, the hypophysis appeared normal in size and shape. For microscopic examination, two sections were cut transversely across the gland. There appeared to be the usual relation between the types of cells comprising the glandular portion, but at the lateral inferior margin of the pars anterior there was a sharply circumscribed nodular collection of basophilic cells measuring about 2.5 mm. in diameter. The structure of this nodule differed from normal structure in that all of its cells were basophilic. They were arranged in cords with the usual amount of stroma. Although the nodule did not appear to be encapsulated, there was evidence of compression atrophy of the surrounding glandular tissue (figs. 1 and 2).

Thyroid: The thyroid was moderately enlarged (49 Gm.), but regular in outline. Its shape was not abnormal; the lobular markings could be distinguished, and there was a moderate amount of colloid. Early adenomatous change could be made out. On histologic examination the gland appeared to be well involuted,

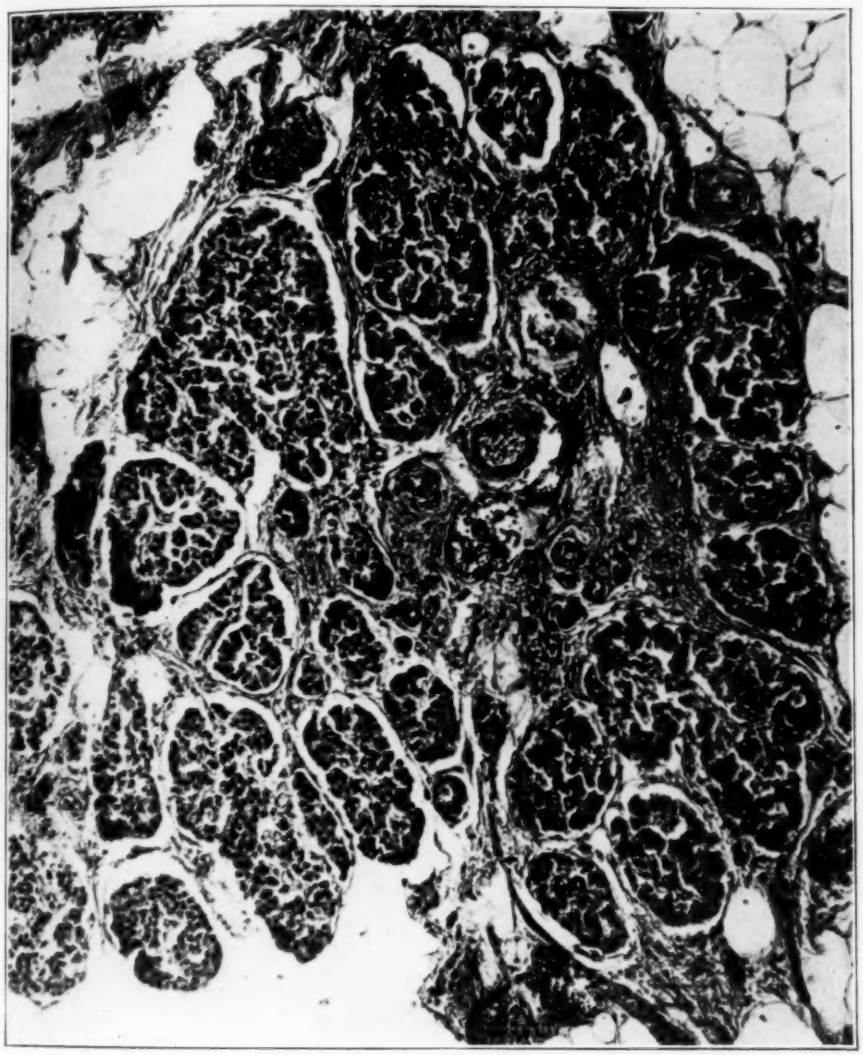


Fig. 3.—Photomicrograph from the pancreas, showing an isolated mass of islets without the normal intervening enzyme-secreting acini.

with unusually well defined lobular markings and a diffuse increase in fibrous connective tissue. The acini were fairly large but varied in size and shape, often appearing confluent with lobules separated by short spurs. The epithelium was flattened, and there was no excess of lymphoid tissue. Several small cellular

collections with the formation of giant cells were noted, in the process of phagocytosis of interacinar colloid. The general picture was that of a recently involuted gland.

Thymus: The thymus was relatively large (24 Gm.) and extended well up into the base of the neck. Microscopically, the organ was well vascularized and showed little evidence of involution. The lobules of lymphoid tissue were large with prominent Hassall's corpuscles, some of which showed beginning calcification.

Pancreas: The pancreas weighed 75 Gm. and showed nothing unusual on gross section. Microscopically, however, examination of tissue from the head of the organ showed an unusually large number of islets. The impression was gained that many of these structures were larger than usual, being visible in the stained slide without magnification. In the periphery of the section there was a clump of more than thirty islets, without any intervening enzyme-secreting cells (fig. 3). At one margin of this group of islets, several small ductules were seen.

Suprarenals: The suprarenals were both definitely enlarged (20 Gm.). Both appeared normal on gross section. Histologically, there was no abnormality of structure.

Ovaries: Both ovaries were decidedly larger than usual, the right measuring 6.7 by 4 by 3 cm., and the left 5.9 by 3.7 by 2 cm. In the right organ there were one large solid and two smaller cystic corpora lutea. Numerous small follicular cysts were present in both glands. The increase in size of these organs was not due to a few large cystic structures but apparently to actual increase in stroma. Microscopically, there were one large corpus luteum with a small central hemorrhagic area and several smaller ones showing varying stages of organization. A number of small retention cysts and several immature follicles were present.

Uterus: The uterus was of average size and hyperemic. The endometrium was thin, hemorrhagic and roughened. Histologically, the cervix did not show pathologic change. The endometrium was thin and the superficial layer desquamated. The glands were straight and not hyperplastic, and there was no evidence of degenerative change. The surface of the endometrium was covered by a hemorrhagic exudate of fibrin, red blood cells, mononuclear cells and desquamated stroma and epithelium. Thrombosis of dilated veins was noted in this superficial layer.

COMMENT

The particular interest in this case centers about the fact that while the ovaries, thyroid and suprarenal cortex were decidedly hypertrophied, the thymus uninvoluted and the islet tissue in the pancreas possibly hypertrophied, the only truly neoplastic growth was the small basophilic hypophyseal adenoma. As already pointed out, the prolonged administration of anterior hypophyseal substance in animals brings about a similar enlargement of these organs, the resultant hyperplasia in the instance of the adrenal cortex being occasionally of the adenomatous variety. Further experimental evidence indicates that, at least so far as the gonads are concerned, the hypertrophy is caused by a hormone elaborated by the basophilic cells of the anterior lobe. It would seem not unreasonable, therefore, that the changes found in this patient may

have been caused by the basophilic adenoma. Such a lesion associated with hypertrophic changes in the gonads was predicted by Teel and Cushing.[5]

It will be recalled that my patient had persistent menstrual bleeding for some months at the age of 9. Unfortunately, the incomplete history does not reveal whether the secondary sex characters were fully developed at this time.

Explanations of clinical pubertas praecox in both male and female and the frequently associated pluriglandular disturbances have never been entirely satisfactory. In the case of pinealoma in boys it has been shown that histologically identical tumors are in some instances associated with full blown pubertas praecox and in others without evidence of premature maturity. Further, marked pubertas praecox is seen without pineal tumor. One is confronted with the same difficulties in the case of the tumors of the suprarenal cortex. It would seem probable that careful examination of the hypophysis in such cases might reveal a basophilic hypophyseal adenoma, at least in some of them. In the light of present knowledge of the function of these cells, such a lesion, when present, might logically be looked on as provocative of such a syndrome.

5. Teel, H. M., and Cushing, H.: Separate Growth-Promoting and Gonad-Stimulating Hormones of Anterior Hypophysis, Endokrinologie **6**:401 (June) 1930; "Not until the discovery of a hyperpituitary state associated with an adenoma of the basophilic elements will it be possible for us to get at the key of those pituitary disorders which primarily cause disturbances of sex and its secondary characters. Undoubtedly such an adenoma will some day be found" (p. 417).

Clinical Notes

FORCED GRASPING AND GROPING *

DAVID B. DAVIS, M.D., AND FRED P. CURRIER, M.D., GRAND RAPIDS, MICH.

The difficulty with which lesions of the brain are localized presents a problem of paramount importance to even the well trained neurologist. For this reason we feel justified in presenting the following interesting case, which may be compared with thirty-two similar cases that have been reported previously in the literature. In the case reported signs were elicited in the right upper extremity which, in view of previously published work on forced grasping and groping, made a diagnosis of a lesion of the opposite (left) frontal lobe the first presumption. As a matter of fact, forced grasping [1] in either upper extremity is the best neurologic evidence of a lesion of the opposite frontal lobe; pathologic observations [2] made in thirty cases verify this contention.

REPORT OF CASE

History.—Mrs. S., aged 39, entered the clinic on June 24, 1929, complaining of occasional vertigo and numbness and weakness of the right side of the body, including the face, shoulder, arm and leg. The family history for nervous or mental diseases was entirely irrelevant. The patient had been well until five years before admission, when the present condition began.

The menstrual periods began at the age of 13. They were irregular at first, but later became regular. For the past two years, the patient had had much abdominal pain during the periods, and a decrease in the amount of menstrual flow had occurred. The patient was married at 17 years of age; she had had five children, all of whom were living and well. She also had had two miscarriages, the cause of which was unknown. The last child was born six years previous to examination, when she had had a difficult labor, with severe hemorrhage.

The present illness began in November, 1925, with what was called an attack of "influenza." This began with a sore throat and was followed by headache, general weakness and fever, which lasted for about two weeks. She believed that she had never really recovered from that illness, and that since then she had gradually become more incapacitated. She began to be weaker and noticed

* Submitted for publication, Feb. 14, 1931.

1. Janischewsky, A.: Das Greifen als Symptom von Grosshirnläsionen, Deutsche Ztschr. f. Nervenh. **101**:177, 1928.

2. Adie, W. J., and Critchley, Macdonald: Forced Grasping and Groping, Brain **50**:142, 1927. Freeman, Walter, and Crosby, P. T.: Reflex Grasping and Groping: Its Significance in Cerebral Localization, J. A. M. A. **93**:9 (July 6) 1929. Lhermitte, J.; de Massary, J., and Mugnier: Syndrome frontal et signe de la préhension forcée, Rev. neurol. **1**:587 (April) 1928. Schuster, Paul: Autoptische Befunde bei Zwangsgreifen und Nachgreifen, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:715, 1927. Wilson, S. A. K., and Walshe, F. M. R.: The Phenomenon of "Tonic Innervation" and Its Relation to Motor Apraxia, Brain **37**:2, 1914.

the gradual stiffness and weakness in the right lower extremity. Difficulty in using the right arm did not develop until about six months after the occurrence of the "influenza." One day, while she was cooking, the right forearm suddenly dropped on the stove and was burned before she could use the left hand to lift it off. Within a few minutes, sufficient strength had returned for her to use the arm almost normally. She had noticed a continuous weakness and stiffness in the arm since that time, and she had been unable to write with facility for the past two years. Since the early part of the illness, she had not been able to spread a tablecloth. Invariably, when turning from the table, she found the tablecloth gripped in the right hand. During the last four months prior to her admission to the clinic, she had dragged the right leg in walking and complained that it was somewhat stiff.

About one week previous to the examination, she had had what was termed "a spell," which lasted for four and one-half hours and which consisted of inability to talk, though she knew what she wanted to say. The patient had always known the use of objects placed in the right hand (apraxia was not present).

The patient did not complain of headache, but she complained of an occasional attack of dizziness, with a rather marked tendency to fall to the right. She stated that vision in the right eye was not good. There were no complaints so far as the ear, nose and throat were concerned, but there was occasional pain in the chest and shortness of breath. She had lost 10 pounds (4.5 Kg.) during the past year. There were no gastro-intestinal symptoms. At times during the past two years, frequency and slight incontinence had occurred.

Neurologic Examination.—The patient was 62 inches (157.5 cm.) tall and weighed 123 pounds (55.8 Kg.). There was no loss of memory for past or recent events, and she did not show mental deterioration. Attention and judgment were good. She had no hallucinations or delusions. She was emotionally normal and not jocose.

The patient's gait was that of a person who had a mild degree of right spastic hemiplegia. The heel of the right shoe was built about 1 inch (2.5 cm.) higher than that of the left. The right arm was carried in a semiflexed position. In testing for a Romberg sign, it was observed that the patient had a tendency to fall toward the right, but there was no definite Romberg sign. There was no intention or other tremor of the hands, and on the finger-to-nose test and finger-to-finger test, she did not show ataxia. The grip in the right hand was 20; in the left hand, 30. When an object was placed in the palm of the right hand, there was an active grasping of a reflex nature (fig. 1). The force of this grasping was increased as attempts were made to withdraw the object (fig. 2); if the hand was not disturbed, after about one minute the fingers would gradually relax and the object could be removed. If the attention was directed away from the closed hand, relaxation would take place more readily. The patient complained of this symptom, as she said it caused her much inconvenience. She noticed the difficulty, particularly in attempting to transfer objects from one place to another in her house. Grasping could be evoked merely by stimulating the palm of the hand with the examiner's finger. She could close the hand voluntarily, but she experienced difficulty in opening it. In fact, she could seldom open it immediately without the use of force from her left hand or from the hand of the examiner. Here, too, it was noted that the contraction, or the grasping, would release itself in less time if the attention of the patient was distracted for a moment or two. Even then, the hand usually opened rather slowly. The patient did not have astereognosis, apraxia or aphasia.

The patient's face was symmetrical. Movements of the facial muscles were normal. She wrinkled the forehead normally. The tongue was not atrophied, and all of its movements were normal. The patient moved the palate normally. The muscles of the jaw were normal. The palpebral fissures were equal. The pupils were equal, round and symmetrical; they reacted promptly to light and in accommodation. The consensual reflex was normal. All of the extra-ocular movements were normal. There was no nystagmus. The sclerae were clear. Hearing, taste and smell were normal.

The biceps, triceps, knee and achilles reflexes were increased on the right side. The reflexes on the left side were normal. There was no umbilical reflex on either side.

There were a Babinski and a positive Hoffman sign on the right side.

Fig. 1.—Reflex grasping on stimulation of the palm of the right hand.

Fig. 2.—Tonic perseveration, necessitating the use of the left hand in opening the right hand.

Sensation of pain, light touch, vibration, motion and position and pressure on the tendo achillis were normal.

There was no increase in sweating and no marked smoothness of the skin. Up to the level of the knee, the right leg was colder than the left. There was slight swelling of the right ankle.

The acuity was 6/7.5 in each eye. The fields had normal outlines. The blind spot was normal. Vision was normal to all tests for color. The pupillary reactions were normal. The heads of both nerves showed blurring, with 3 diopters of swelling.

Examination of the ear, nose and throat gave negative results.

Physical Examination.—Examination showed infection of the lower teeth. The thyroid, heart, lungs and abdomen were normal. The blood pressure was 115 systolic and 75 diastolic. The heart rate was within the range of normal.

Gynecologic examination gave normal results, except for slight erosion of the cervix.

Laboratory Observations.—Urinalysis showed a specific gravity of 1.014; the urine was clear, with an alkaline reaction; sugar and albumin were not found; there were occasional white blood cells and epithelial cells. A blood count showed: hemoglobin, 80 per cent; red cells, 2,960,000, and white cells, 9,000. The Kahn test gave negative results. The spinal fluid, which was found to be clear and under normal pressure, gave negative results with the globulin, albumin and Kahn tests, and the colloidal gold curve was 0011000000.

Course.—When the patient was seen in June, about one week after the first visit to the clinic, the signs and symptoms were as before.

She was seen again on July 31, when the reflex grasping had disappeared. She had improved generally, had gained in weight and appeared better physically.

The patient was again seen in the clinic on September 10. At that time, the symptoms were unchanged from those that had been present during the latter part of July, except that she had had two attacks in which there was evidence of aphasia. She was able to say several words in a sentence, but was unable to finish the entire sentence. These attacks lasted for about an hour. The attacks of difficulty in speech were preceded by what the patient described as a drawing sensation in the right hand and the right arm and then in the right leg. There were no convulsive movements of the right arm or of the right leg, and the patient was conscious at all times.

During the summer of 1929, she had had pain in the right side of the jaw and definite pain on opening the mouth. She believed that her eyesight had improved since the previous visit. She stated that she had had insomnia for about ten days prior to the last visit (September 10). She thought that she had gained in general strength and that she was able to "think more clearly." (There was no evidence of difficulty in the mental processes at any of the previous examinations.) She mentioned that she could now walk in a straight line with less tendency to walk toward the right. The forced grasping had not returned. A neurologic examination, however, showed that the sign could be elicited to a certain extent through repeated and rather strong irritations of the palm of the right hand. The last two fingers and the middle finger of that hand could be made to flex somewhat. The other neurologic observations were the same as those made on previous visits.

On October 8, the patient's condition was the same, except that there was still evidence of a definite blurring of 2 diopters of both disks. In the meantime, she had gained about 4 pounds (1.8 Kg.). The hemiparesis remained as it had been on the first visit.

The patient returned on March 16, 1930, and stated that she had not had difficulty with speech or attacks of any sort since Oct. 8, 1929. Because of the increased "clumsiness," the right hand had become still more useless. Also, the right leg seemed more "stiff" than at previous examinations. She was of the opinion that vision was unchanged. A neurologic examination showed only the following changes: The Babinski and Hoffman signs were no longer present. There was still no umbilical reflex or ankle clonus. Forced grasping had returned to a certain extent. One could irritate the palm of the right hand and produce partial flexion of the last three fingers. The patient could quickly grip a pencil voluntarily, and showed considerable strength in doing so, but had difficulty in releasing the grip and often had to use the left hand in doing so. On questioning, she stated that she had noticed difficulty in relaxing a flexed right thigh. She

had also noticed that when the right lower extremity was fully extended, it was difficult for her to flex it. An examination of the eyes at this time showed no contraction of the visual fields, and there was still a bilateral choked disk. At this time, the patient gave her consent to the making of an encephalogram (figs. 3 and 4).

After the encephalogram had been taken, the patient refused to undergo an operation, but consented to deep roentgen therapy, which was given in six treatments. Within ten days, the patient seemed to feel better, took a greater interest in things about her and walked about the ward with more ease than at any time during the preceding year. She could also use the arms and hands to fix her hair or hat. Examination showed that she could open and close the right hand

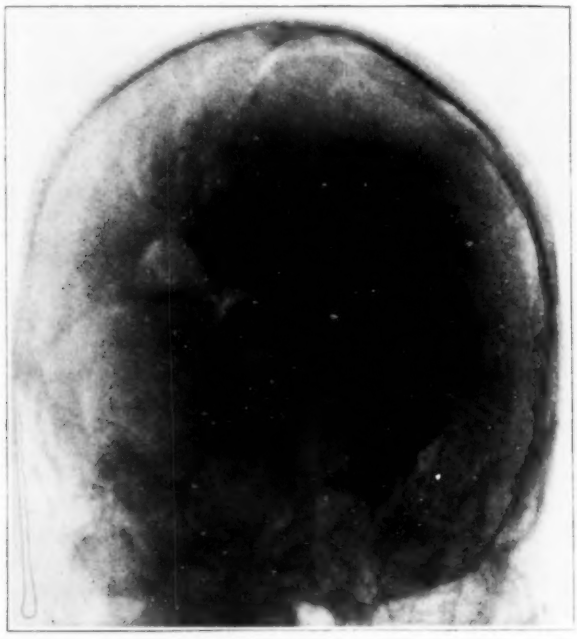


Fig. 3.—Anteroposterior film, showing the lateral ventricles and the superior sinus pushed to the right.

easily and that no forced grasping or tonic innervation was present. The reflexes were equal and normal on the two sides. There was no Hoffman sign, but a Babinski sign was definitely present on the right. There were no headaches, and she could see well enough to read a newspaper. There was less swelling of the optic disks.

The patient was last seen on Dec. 2, 1930. The gait was more spastic than at the time of the previous examination, and she walked by swinging the whole right lower extremity in a semicircle. The deep reflexes in the right arm and leg were slightly exaggerated. There were also a Babinski sign and ankle clonus on the right, but no Hoffman sign. Sensation was normal on both sides. On examination of the cranial nerves there were no unusual observations, and there was no choking of the optic disks.

COMMENTS

This case presents all the usual clinical features of a tumor in the left frontal lobe plus the two new conditions under discussion, namely, reflex grasping and tonic perseveration. The first condition noticed in our case was that of forced grasping. This occurred on stimulation of the palm of the hand or on placing a foreign object in the palm of the hand. On so doing a reflex closure of the hand occurred, apparently independent of the volition of the patient. To all appearances, the speed of closure was independent of the type or strength of stimulation. At the time of the first examination, the hand closed rather quickly on stimulation of the palm, but during the later months of observation, the hand closed slowly on stimulation. The hand remained closed for some time, and then a slow relaxation

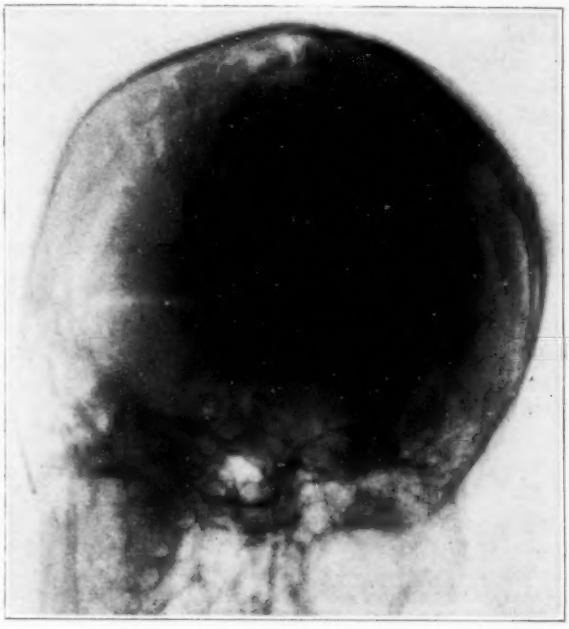


Fig. 4.—Postero-anterior film, showing the dark area of the tumor. Note the small posterior horn of the left ventricle.

of the contracted muscles began. Any effort to remove the object from the patient's hand only increased the stimulation and the strength of contraction. At times, a light touch and at other times stronger stimulation were necessary to produce a closure. The latter was noted during the last month of our observation of the patient.

The second condition, or sign, was that of tonic perseveration, or the persistence of the muscular contraction for more than the ordinary length of time after voluntary initiation. Not only did the tonic perseveration persist after voluntary closure of the hand, but at times it persisted after reflex stimulation of the palm. Our observations agree with the opinion of Adie and Critchley,[3] who expressed

3. Adie and Critchley (footnote 2, first reference).

the belief that tonic perseveration could take place after either voluntary closure or reflex closure of the hand. They further believed that many cases of reflex closure have been overlooked, but have been reported only as cases of tonic innervation.

In our case we noticed that during the earlier observations the patient could voluntarily open the hand in the same length of time after reflex grasping as she could in later observations after voluntary closure. As the tumor became larger, reflex grasping disappeared, but tonic perseveration after voluntary closure remained. This does not agree with the views of Adie and Critchley [3] when they stated: "Further observations will perhaps confirm our surmise that a lesion that produces reflex grasping, with persistent contractions, is always more extensive and more destructive than one that produces persistent contractions after voluntary innervation alone."

In this discussion, one must take into consideration the fact that the reflex, when found pathologically, is not so constant as one might expect; that is, at times light stimulation of the palm will not bring it out, and one may even have difficulty in eliciting it with strong stimulation. As with the knee reflex, the mental state of the patient may influence the type of response obtained. This may be particularly true in that phase of the response that deals with tonic perseveration and the relaxation that takes place with distraction of the attention.

It has been assumed that an infant who has progressed to the point where voluntary contraction is possible will still have tonic perseveration. This is frequently seen in children who have reached the creeping stage and who carry an object from one place to another, apparently wishing to pick up a second object without realizing that the first is in the hand. However, there is room for doubt as to whether the child who clings to the object while creeping is manifesting the same mental mechanism as the adult, who, by volition, is attempting to open the hand flexed in tonic perseveration. Should it be called tonic perseveration when there is some question as to the desire on the part of the infant to release the object? A child's attention in performing an act or a series of similar acts is momentary, to say the least, and only well controlled observations of a number of infants at various ages would be of any real value in answering the question. One can see no real reason why voluntary extension of the hand would not be developed simultaneously and to an equal degree with voluntary flexion.

Numerous theories have been advanced as to the causal factor in forced grasping and tonic perseveration.[4] The theory most often offered as an explanation is the following: Such a reflex as forced grasping, found normally in the infant, is supposedly due to the control exerted by those basal nuclei that are myelinated at birth. The exact mechanism responsible for this reflex in infancy is far from solution at present. To use Pavlov's terminology, one is sure that in the newborn infant volition has as yet played no part in conditioning the reflexes present. It is assumed that volitional experience is laid down in the higher cortical centers. The most common theory offered as regards the pathway of the reflex is as follows: The peripheral stimulation follows along the sensory nerves to the sensory tracts in the cord, thence to the thalamus and globus pallidus. From there it may pass by motor tracts to the brain stem and the spinal cord and, finally, to the group of muscles innervated in the reflex act. These reactions can

4. Adie and Critchley (footnote 3). Janischewsky, A.: A Case of Pseudo-Parkinson's Disease, with Pseudo-Bulbar and Pseudo-Ophthalmoplegic Syndrome; Also Some Consideration on the Pathology of This Disease, Rev. neurol. **17**:823, 1909; footnote 1. Wilson and Walshe (footnote 2, fifth reference).

take place by this path because the paleostriatum, or the globus pallidus, is myelinated at birth, while the cortex and neostriatum (caudate nucleus and putamen) do not become myelinated until after the fifth month of extra-uterine life.

As the infant begins to exert voluntary control of the movements of its hands and fingers, one must consider, in addition to the aforementioned pathway, association tracts from the basal nuclei to the ideomotor areas in the frontal lobe, as well as further association tracts with the motor center for the fingers and hand in the motor cortex (precentral gyrus). There are still further association pathways between the motor center for the hand and the basal nuclei. The cutting off of the pathway between the ideomotor center and the basal nuclei might account for the appearance of this reflex of forced grasping while still retaining the voluntary ability to open and close the hand (pathway from the ideomotor to the hand area in the motor cortex).

SUMMARY

1. This is the only case presented in recent years showing a combination of tonic innervation and forced grasping in the same person.

2. The tonic innervation persisted after the total disappearance of the reflex, and was noted after voluntary closure of the hand.

3. The case presented, with other clinical observations, a lesion of the frontal lobe on the contralateral side.

4. The clinical diagnosis was verified by encephalograms.

THE OCCASIONAL FULMINATING COURSE OF ENCEPHALITIS EPIDEMICA*

WILLIAM S. MIDDLETON, M.D., MADISON, WIS.

The conspicuous and distressing sequelae of encephalitis epidemica have led to the growing belief in its protracted course. The frequency with which the initial invasion is overlooked and the true status of affairs recognized only by the so-called postencephalitic manifestations, has contributed still further to this professional judgment. Yet cases of a fulminating character do occur and must be evaluated before a comprehensive idea of the course of encephalitis can be gained. Hence the following case is reported.

REPORT OF CASE

History.—R. S., a white woman, aged 20, was admitted to the University Infirmary on Jan. 29, 1924, with the complaints of sore throat and headache. These conditions had existed in some degree for three days, but there had been no incapacity for ordinary duties. On the morning of admission the general malaise had first become troublesome and the throat was decidedly worse. The past medical history was irrelevant, except for the operations for repair of a harelip and cleft palate. The social and family histories had no bearing on the existent condition.

Physical Examination.—At the time of admission extreme apprehension and nervousness were noted. The scar from the operation repairing the harelip was

* Submitted for publication, Jan. 19, 1931.

* From the Department of Medicine, University of Wisconsin.

observed. There was marked fetor oris. The palate was cleft, and the pharynx was injected. The tonsils were cryptic and covered with a whitish exudate. The temperature at this time was 100.8 F.; the pulse rate, 104, and the respiratory rate, 22.

Course.—On the morning of the succeeding day the patient could not be aroused. Convulsive seizures had not been noted during the night. The skin was flushed. A marked tâche cérébrale was elicited. The faucial pillars were boggy and edematous, and a streak of whitish exudate was noted at the left free edge of the cleft palate. A general physical examination showed no other abnormality. A neurologic examination showed irregularity of the pupils, but a normal reaction to light. The tendon reflexes were exaggerated, the right being greater than the left. Abortive right ankle clonus and right patellar clonus were observed. Bilateral Babinski reactions were elicited, the left being somewhat less typical than the right. The Chaddock and Oppenheim signs were likewise bilaterally positive. There was some incontinence of urine. The blood pressure was 118 systolic and 78 diastolic.

The blood count on the second day was as follows: hemoglobin, 80 per cent; erythrocytes, 4,860,000; leukocytes, 27,000; polymorphonuclear neutrophils, 92.1; basophils, 0.1; lymphocytes, 4.5, and large mononuclears, 3.3 per cent.

Lumbar puncture was performed twice on the second day, and on both occasions the fluid was clear. At 11:30 a. m. examination of the spinal fluid showed 3 cells per cubic millimeter; at 7:45 p. m., 10 cells per cubic millimeter; these cells were of the lymphocytic order. Urinalysis showed a trace of albumin and occasional red blood cells. A culture from the throat taken on the first day showed streptococci and staphylococci. The nasal culture showed staphylococci. On the second day the temperature ranged from 98 to 104 F.; the pulse rate, from 96 to 120, and the respiratory rate, from 22 to 36.

Breathing became more labored, and the stupor apparently deepened. Later, on the afternoon of the second day, conjugate deviation of the eyes to the left was noted, and there was apparent incoordination of the muscles of both eyes with slight nystagmoid movements.

On the morning of the third day the muscle tone seemed definitely less marked; the conjugate deviation of the eyes had disappeared, and there was no Kernig sign. The disappearance of the stiff neck was interpreted as depending on a lessened resistance of the cervical muscles. Throughout the day, however, the coma became rapidly deeper and at 4 p. m. a convulsion, which began in the right side of the face and which lasted for one minute, involved the face and both arms. Succeeding this episode, at ten-minute intervals on three separate occasions, convulsive movements of the upper extremities developed. Thereafter the patient became very cyanotic and Cheyne-Stokes respiration developed. The pupils became miotic with only slight reaction to light after the onset of the convulsive seizures. Furthermore, the tendon reflexes were diminished, and a Babinski sign could no longer be elicited. The patient died following the third convulsion. The temperature on this last day ranged from 102.6 to 105 F.; the pulse rate from 120 to 148, and the respiratory rate from 36 to 46.

Necropsy.—A necropsy was performed in which the only significant changes were determined on histologic study of the sections of the brain. Prof. C. H. Bunting gave the following report:

Sampling sections were cut from the stem of the brain, the cerebral cortex and the cerebellum. Although in general the lesions were present in all, those in the cerebral cortex were most marked.

Over the cortex the pia mater showed a marked swelling of its fibers, slight edema, marked congestion of the vessels and a slight lymphoid perivascular infiltration. The vessels of the cortex were much congested; the perivascular spaces showed edema and occasional small hemorrhages, but particularly a cellular exudate, which, though in the main consisting of lymphoid and mononuclear cells, was not lacking in polymorphonuclears. This exudate was most marked about the larger vessels; however, lymphoid cells were found about the smallest capillaries and even in pericellular lymph spaces. An occcasional leukocyte was also present in the pericellular spaces. Ganglion cells were well preserved; yet they appeared somewhat shrunken and their Nissl bodies had suffered chromatolysis.

COMMENT

The case was interesting by reason of several unusual circumstances:

1. The initiation of the fatal illness by a frank tonsillitis.

2. The absence of objective neurologic manifestations until approximately thirty-six hours before death.

3. The possible relationship of a congenital deformity of the palate to the rapid development and the progression of neurologic manifestations. This circumstance would presuppose a pharyngeal or tonsillar origin for the virus responsible for the development of the lesion of the central nervous system.

4. Finally, confirmation of the clinical diagnosis by the pathologic examination in the complete histologic picture of an encephalitis.

This case is presented merely in the hope of emphasizing the occasional fulminating course of encephalitis epidemica, the residua of which have led the medical profession at large to consider the condition as rather a subacute or chronic disease.

SPECIAL ARTICLE

SCHIZOPHRENIA

REVIEW OF THE WORK OF PROF. EUGEN BLEULER *

MANFRED BLEULER, M.D.
WHITE PLAINS, N. Y.

Since coming to the United States I have had the valuable experience of realizing that the conceptions of schizophrenia are very different here from those held in our clinic at Burghölzli. In the following pages I shall try to emphasize the points of difference and to cover briefly the views held in common here and in Switzerland.

My father considered it an important step in the understanding of schizophrenia to separate the primary from the secondary symptoms. His purpose was to discover, among the confusingly large number of schizophrenic signs described by Kraepelin, the ones that were present in every case and had to be regarded as the basic difficulties from which the secondary signs developed. This development of the secondary signs on the structure of the primary lesions he considered as due to normal environmental irritations and to normal psychologic and physiologic mechanisms. For the sake of clarity, this conception of schizophrenia may be compared with the general conception of any medical disease. For instance, in rickets, the lack of calcification, halisteresis, and changes in blood chemistry represent primary signs, and the various deformations due to mechanical influences on the tender bones represent secondary signs.

Therefore, the first aim of my father's study was to attempt to understand at least the secondary signs of schizophrenia, whereas in the past, all signs had been equally enigmatic. Specific disorders, both in association and in affectivity, are the basis of his morbid picture of schizophrenia.

DISORDERS IN ASSOCIATION AND AFFECTIVITY

I shall begin with the associative disturbances. In normal thinking one has to choose constantly from among an immense number of possible associations that have been created by custom, similarity or

* Submitted for publication, Oct. 28, 1930.
* This paper was read and approved by Professor Bleuler.
* Read at a Monday Evening Meeting at Bloomingdale Hospital, December, 1929.

causality. This selection is guided by a goal idea (Zielvorstellung) which is loaded with affectivity, or, to speak more exactly, it is guided by a multiplicity of these goal ideas. When I think of water in making a chemical examination, I associate the formula H_2O and the atomic weights. When I am on a mountain trip and become thirsty, I think of water in connection with a ravine or gulley where I may find a refreshing stream. This mechanism of selection does not operate in a schizophrenic patient who writes in a description of a trip: "The mountains are lovely in the clear oxygen."

In schizophrenic thinking the associations no longer seem to follow the same principles as in normal thinking. They are no longer connected by a final aim, and suddenly and without apparent reason they deviate from the direction which in a normal person is given precedence by the topic and aim of the central thoughts. Suddenly and strikingly they are apt to leave the primary topic and to wander off in hidden pathways.

Examples of this deviation can easily be found in nearly everything that a schizophrenic patient says or writes. The example usually given at Burghölzli is the answer of a schizophrenic patient to the question, "Who was Brutus?" He replied, "Brutus was an Italian." A normal person would have said, "Brutus was a Roman." By his answer this patient showed a perfect understanding of the problem and gave the right association as to place, but he failed in the time association, which automatically would occur to every normal person.

A few days after his admission to our hospital, a schizophrenic patient wrote:

Dear Mother:

I write on a paper. The pen which I use is from a factory named Perry and Co. I imagine this. Above the name, Perry & Co., there is written on the pen "City of London." But not the city. The City of London is located in England. I learned this in school. I always liked geography there. . . .

A normal writer would certainly tell about his condition or anything else of interest to his mother. Here one can find no deeper motive than to write a letter. The only common feature of all the ideas in this letter is that they have some loose connection with the objects around the patient and are written down in the form of a letter.

This is merely a general and rather vague description of the schizophrenic associations. Quite a few more specific forms of schizophrenic associations have been separated and described. I shall here mention only the most important ones.

1. Two unrelated ideas in the patient's mind are connected, in spite of the fact that there is no logical connection between them. There is a particular tendency to make an incorrect causal connection in this

way. I asked a patient, "Why are you crying?" and he answered, "Because you are dressed in black," although he had been crying long before he saw that I was dressed in black. Something about a ship was mentioned to a patient who was preoccupied with religious ideas, and he responded, "God is the ship of the desert," thereby combining a queer association to the word ship with his idea of God.

2. Several different ideas are combined in a process named condensation. A patient, looking down on the lake of Zurich, and noting both steamships and sailboats, spoke of "steamsails."

3. The schizophrenic patient often uses a symbol on an occasion when the normal consciousness would have suppressed it and kept only the real object in mind. A schizophrenic woman expressed the fact that she was pregnant by the words, "I hear a stork clapping in my body." A Protestant patient whose love affair with a Catholic girl had failed on account of the opposition of priests hated "black papers" and destroyed them, since for him they were symbols of priests.

4. General, vague notions are often associated where a concrete statement is the normal procedure. Every psychiatrist has heard schizophrenic patients reply, "Because I hate to be in the hospital," when asked the reason for a definite aspect of their misbehavior. Here the general and vague feeling of uneasiness incident to being in the hospital is given as the reason for a quite inappropriate action.

5 and 6. Alliterations, like "boots-beauty," and mediate associations are both found frequently in schizophrenia. As an example of mediate association, a schizophrenic patient remembered his cousin when wood was mentioned, because wood had released the association "wooden coffin" and because the cousin was dead. In manic states these special associative disorders approach the manic flight of ideas and therefore become less characteristic. However, these associative disorders are characteristic of schizophrenia when they are not connected with overtalkativeness, but only with short and stereotyped associations.

These disorders of association are present in nearly all cases of schizophrenia, but they differ greatly in degree. The degree varies not only from patient to patient but in the same patient from day to day, from hour to hour and from topic to topic. In order to make these disorders in association manifest we frequently use psychologic experiments, of which the Jung and Rorschach are the favorites. Jung's association test is used not only for psychoanalytic purposes, but for considerations with regard to form. A patient associated the word "thread" with "heart" and gave the explanation, "because two hearts are connected by a thread." Another reacted to "hay" with "means of entertainment for cows," and was serious in this reply.

Rorschach's form-interpretation test elicited the following: To table 9, a schizophrenic patient answered, "It is the principle of good defeating the principle of evil." This answer shows the tendency toward both general abstractions and mediate associations. The tendency to miss quite natural associations and to put unnatural ones in their place is illustrated by the answer "Four flies" to table 1, referring to four small points outside the main picture.

Disorders in affectivity coupled with the aforementioned associative disorders are among the primary signs of schizophrenia. As a matter of fact, my father believes that associative and affective disorders are identical, but seen from different angles. However, this is not the place to discuss that question.

Contrary to the older belief, he regards indifference to environment and lack of affective modulation as not due to a primary destruction of all feeling. In most schizophrenic patients he finds at times the evidence of strong, natural and well modulated feelings, even in chronic and demented cases. A special kind of splitting of the feelings is much more general and characteristic and finds its clearest expression in ambivalence. For example, a patient who is saying goodbye to her physician as he is leaving the hospital, curses him loudly. But she interrupts her violent profanity several times in order to whisper her gratitude for the doctor's kindness to her and to beg him not to mind her bad temper. Another example of this ambivalence is found in simultaneous laughing and crying and in paramimia, in which the patients' features do not correspond to the emotional content of their thoughts. Complexes of feelings can be split off so far that they seem strange to the patient, and he can no longer recognize them as part of his own personality. So it is a frequent complaint of the schizophrenic patient that some one else feels or thinks in him, that some one else takes possession of his tongue to speak with it, or of his face to laugh with it.

This splitting off of complexes of feelings is regarded as the basis of the voices that are the most common kind of hallucinations in schizophrenia. In some manifestations of voices the first stage is the feeling that a thought is unnatural, as, for instance, the thought that a conscious action of the patient is a sin. In the next stage the patient no longer feels sure whether the thought, "I am a sinner," is a strange thought or a voice in his head. Finally, he hears the word "sinner" quite distinctly from the outside.

My father thinks that the disorders in association and in affectivity here described must be considered at the present time as the most important and widespread primary lesions in schizophrenia. Not only are they characteristic, but they tend in a wholly opposite direction from

that found in other mental diseases, particularly in the organic group, in epilepsy and in the manic-depressive psychoses. In manic-depressive patients, associations and affects are centralized, and work together to a higher degree than in normal people, while in schizophrenic patients exactly the opposite is true. On the other hand, important functions like perception, memory and intelligence are intact in schizophrenia, whereas in other diseases they are primarily affected.

SECONDARY SIGNS

I shall now proceed to the secondary signs, which include most of the signs described by Kraepelin, such as autism, delusions, illusions of memory, some of the hallucinations, negativism, stereotypies, mannerisms and most of the catatonic signs. For the explanation of all these phenomena my father has utilized the mechanisms that are true also for the secondary elaborations of normal psychology and based on the primary trouble. The root of autism, for instance, is regarded by him as the tendency to make reality inoffensive. The patient splits reality off from his consciousness and escapes into his imagination. It is a like mechanism that drives some types of monks into their monasteries, some saints into the desert and some scientists within the walls of their laboratories. Not only is reality split off, but the patients fulfil their conscious and unconscious wishes in their secondary signs.

This explanation is applicable to phenomena that at first sight seem to contradict it, as, for example, delusions of persecution. The persecutions can be a direct fulfilment of sex wishes, particularly in the case of women. Frequently, they interpret the patient's problems in such a way as to render her innocent and worthy of sympathy. The persecutions conceal the belief that everything that is unfavorable to the patient will be eliminated.

Numerous analyses of schizophrenic patients and schizophrenic signs have been made at Burghölzli, the clinic of Zurich. The explanation of the secondary signs forms the major part of my father's study of schizophrenia. I do not need to say more about these mechanisms in schizophrenia, for studies concerning them have been undertaken and advanced in the United States more than anywhere else in the world.

I will add only that my father considered certain types of deterioration more as psychologic reactions than as direct expressions of an organic condition. Formerly in European clinics, deteriorated schizophrenic patients had been compared to vegetables without feeling or intelligence and with no signs of life other than those of mere vegetative existence. By means of many examples my father was able to show the error of this conception. For instance, quite suddenly, a deteriorated schizophrenic patient will make a complicated plan of escape. Or a

patient who has stood inactively in a corner for months may all at once give evidence of knowing the details of happenings in the physician's family during this time. On one occasion a patient congratulated me on having passed a medical examination, though no one was able to explain how he knew about it. A notable change in environment, such as the experience of a physical disease, or a long and serious talk by the physician, may result in bringing a patient who seemingly had no affect out of his state of inaffectivity. When my father was director of a mental hospital in the country an epidemic of typhoid fever occurred. Since there were neither telegraph nor railroad facilities at that time and he was without adequate nursing help, he gave nursing duties and responsibilities to some of the chronic schizophrenic patients. They assumed these duties and acted as normal people would. After trained nurses arrived many of them fell back into their customary state, but for a few the experience was a step toward positive improvement. My father also described deteriorated schizophrenic cases in which a senile process freed the affectivity that for many years had seemed to be lost. I may mention here also that in Rorschach's form-interpretation test deteriorated patients often show results similar to those in beginning cases. Because of these and other experiences my father is inclined to look on schizophrenic dementia as a secondary sign to a certain extent, and to attribute a great rôle in its production to environmental factors.

On the other hand, there are certain symptoms which he considers as more or less primary and in which he is inclined to deny the importance of psychogenic roots. Among them are certain kinds of stupor and confusion, which give the impression of being organic and which disclose an edema of the brain and evidence of increased intracranial pressure at the autopsy. There are also certain forms of hallucinations which seem to have a more direct organic basis, particularly the auditory hallucinations of simple sounds, of gunshots and of roaring, and some somatic hallucinations. These are similar to the hallucinations observed in toxic psychoses, and psychologic analysis fails to discover their roots. Therefore, they seem to represent a more direct expression of an organic schizophrenic process.

ETIOLOGY

As to etiology, my father always emphasized that it is easy to explain the secondary signs by means of psychologic mechanisms, but that, up to the present time, all attempts to arrive at the etiology of the primary disorder have been unsuccessful. For him the psychologic explanation applies only to the secondary signs, and he thinks that it is

important for further research to realize that the etiology of the basic disorder is still enigmatic.

His first reason for this attitude is the fact that in his analyses of schizophrenic patients he could find neither abnormal inborn tendencies nor environmental difficulties of a more marked character than those to be found in psychoneurotic patients or in normal people. For him, sex or environmental difficulties must be an insufficient explanation for the origin of the psychosis, as long as it is evident that the same difficulties exist for normal people.

It seemed strange to me, because of this training, to find on the statistical cards of American hospitals that questions dealing with the etiologic factors in schizophrenia were answered by data such as: "unhappy love affair," "worry over venereal disease," "reduction in salary," etc. In Burghölzli we should answer the question with a stereotyped interrogation point, and to such data as those cited we should give the greatest importance as affecting the content of the psychosis. We should assume, moreover, that such experiences might cause emotional reactions necessitating institutional care for schizophrenic patients who had been able to live outside before. We have observed frequently and clearly that the unhappy love affair or the sudden failure in business was the sequel of the beginning schizophrenia, but we have never had reason to believe that schizophrenia was the sequel of the failure in business or of the unhappy love affair.

Such observations often have practical significance. The physician's statement that the mental illness resulted from environmental factors might call for the payment of compensation by insurance companies. In Burghölzli, expert opinions are often called for, and on such occasions careful study is given the anamnesis. I remember a case of an acute catatonic episode which happened during military service. At first it seemed likely that the mental and physical strain of the service had caused the attack. But it was demonstrated that long before the onset of the episode the patient had shown most serious signs of schizophrenia, such as stereotypies, affectless and senseless ideas of reference, etc. In such a case it was considered fair that the insurance company pay compensation for the period of the acute episode, but not for the subsequent course of the disease, an attitude that has been developed in Burghölzli, particularly by H. M. Maier. In most cases we do not feel that this attitude is unfair to the patient, since we believe that the payment of compensation in schizophrenia, just as in many other diseases, works definite harm in the progress and therapy of the disease.

A further reason for not being satisfied with psychologic explanations of the etiology of schizophrenia was to be found in the experience

of the last war. During those four years, both the soldiers at the front and the people at home were subjected to many forms of severe psychologic strain, yet the number of schizophrenic patients was not increased in any European country.

Apart from these negative reasons for not accepting merely functional causes, there are quite a few positive ones. It is true that up to the present time regular and specific anatomic changes have not been proved, but the lesions that have been reported should not be wholly neglected. Quite frequently, clinical somatic signs appear in schizophrenia, such as vasomotor disturbances, unexplained changes in weight, pupillary signs, epileptiform catatonic spells, leukocytosis, albuminuria and even anuria. Deaths are even thought to have resulted from the schizophrenic process. Again and again when schizophrenic patients have died in acute episodes the observations in the clinic and in the autopsies have been insufficient. Cases of this kind which have occurred at Burghölzli have recently been published by Scheidegger.

One factor is definitely regarded as playing an important rôle in the etiology of schizophrenia—heredity. The exceedingly painstaking and scrupulous studies of Ruedin and his school prove this influence. However, heredity does not seem to explain the disease sufficiently. The rôle of heredity in schizophrenia is not nearly as clear and constant as it is in hemophilia or in Huntington's chorea. My father has been at pains to insist that as yet we do not know that schizophrenia is an etiologic entity and that heredity plays a rôle in all forms of it. There are many other difficulties and problems that cannot be discussed here. But those noted are the most important reasons why most European psychiatrists regard the functional theories as insufficient to explain the primary disorder in schizophrenia. The difference of opinion between America and Europe on this point is striking.

The conception of schizophrenia that I have attempted to summarize met with severe criticism fifteen years ago. At that time criticism was brought to bear on the psychologic aspects of it, while the organic aspects were not discussed. The existence of the unconscious, of symbols and of complexes was denied. It was maintained that there were neither feelings nor complexes in a patient with advanced schizophrenia, and that such a patient was merely empty. The direct statement was made that the study of the content of a psychosis could add nothing to the further understanding of it. Moreover, it was considered unscientific to study such nonessentials as the emotions of a patient. But the main objection related to the classification of schizophrenia. It was objected that schizophrenia contained too many clinically unlike pictures, and that one half of the mental cases in institutions could not

be grouped together into a single classification. Yet my father makes this grouping, and I will summarize briefly his reasons:

1. In all cases of schizophrenia he finds primary signs present that are not found in other mental diseases.

2. In schizophrenia he finds many functions always intact that are impaired in other diseases.

3. In schizophrenia he finds that the course does not necessarily progress to dementia; on the contrary, he emphasizes the possibility of a favorable outcome. I shall refer to this later when I discuss therapeutic measures. Yet the courses in all cases have traits in common, and his discovery of these traits in common has been an additional reason for a single classification.

My father has always maintained that social recoveries not only occur but are extremely frequent in schizophrenia. After their episodes, many of his schizophrenic patients have had no difficulty in living out their lives away from an institution and were useful members of their communities. He has held for a long time that many schizophrenic patients are never recognized as such and are never hospitalized. However, he makes a sharp distinction between social and medical recovery. It is well known that after discharge many patients are schizoid psychopaths who have to do simpler work than formerly. But other discharged patients are quite normal or even brilliant, from a social point of view. My father has shown that even in these cases a careful medical study will usually reveal some marks of the disease in a medical sense.

I remember a head nurse of a ward who performed her duties well and was liked by every one. One day, however, she showed a rather peculiar attitude toward an eczema which she had. She seemed to be ashamed of it, and did not want to be seen by other nurses while being treated. Finally, she confessed that she had many delusions about the eczema and that the delusions persisted, although she recognized them as such. She admitted that fifteen years before she had been a patient in a mental hospital. The records of the institution revealed that she had suffered from an acute catatonic episode at that time. She had moved to another part of the country and succeeded in keeping this episode a secret. Later she brought me a pair of scissors which she had stolen from one of the nurses during her illness in order to have a means of committing suicide. She had managed to carry them on her person ever since then. On several occasions she had left home without the scissors, but, feeling uneasy, had gone back for them. She did not feel sure of herself without them. She gave me the scissors because she was afraid of committing suicide in a new episode. All this was found in a person who had made a brilliant social recovery, and who at this time was carrying on complicated duties.

I became acquainted with another patient who went to a general hospital for an operation for hernia. When he refused to discuss a scar on his forearm I became suspicious. Finally I learned that he had hurt himself in a psychotic episode thirty-five years before. The institution, which had classified him as a characteristic catatonic, had looked on him as having a hopeless case. After he had been discharged as unimproved, he went home, took over the management of his father's farm and carried on successfully. He married and had several children and was a respectable citizen of his village. I spoke with his relatives and none of them had any doubt as to his mental soundness. A careful examination not only revealed schizophrenic traits in the psychologic tests, but uncovered the fact that this man sometimes went to the woods at night in order to speak with voices. He added that many other people in his village were somewhat superstitious.

Such cases as these have caused my father to feel that failure to find traces of schizophrenia in all socially recovered cases may perhaps be due to insufficient and inadequate study. Therefore, he does not think that the common trait in the course of schizophrenia is a continuous process which necessarily leads to dementia. But the general direction of the disease is toward this quite peculiar and characteristic terminal state. The progress of the disease may be arrested at any time and extensive improvements occur. But every acute episode leaves a mark on the patient's personality, and, like every progression in a chronic state, is a step toward this highly specific kind of dementia. The disease does not have to progress, but, if it does, it always moves in the same direction.

4. A fourth reason for a general classification of schizophrenia is the fact that a person may have several forms of the disease consecutively. For instance, after recovering from a catatonic episode, a paranoid state may develop in a patient many years later. Or a hebephrenic picture may change into a catatonic one from one day to the next.

5. This broad conception of schizophrenia has been checked and substantiated by the investigations in heredity of Ruedin's school. For example, they showed that the paranoid forms, which sometimes were classified under a separate grouping, have the same heredity as other forms. In contrast to this, they show that the manic-depressive psychosis has a different heredity.

However, my father has never maintained that schizophrenia is a morbid entity like dementia paralytica. He believes that up to the present time all forms of schizophrenia must be classified together clinically, because of common traits in their course, and particularly in their symptoms. But he considers it a mistake to assume for this

reason that all forms have a common eitology as well. He has always been hopeful that future research in etiology will make it possible to divide schizophrenia into natural groups. For that reason he has used the term "groups of schizophrenias."

DIFFERENTIAL DIAGNOSIS

If I were asked to formulate the point of view in our clinic with regard to the differential diagnosis, I would prefer to do so in connection with one definite problem, for example, the differential diagnosis of schizophrenia from the manic state of the manic-depressive psychosis. Most of the older psychiatrists called every patient a manic who was excited, cried and laughed, kicked the doors and demolished the furniture. It was one of Kraepelin's most valuable demonstrations that these manic states occur in nearly all mental diseases, from dementia paralytica to epilepsy, and from hysteria to catatonia. He was the first to show that the conception of mania has prognostic value only when applied to cases which present overactivity, flight of ideas and euphoria, and which lack signs of other diseases. My father subjected the great number of Kraepelin's differential diagnostic signs to inquiry, and reduced most of them to the presence or absence of primary schizophrenic disorder. In his clinical lectures he was accustomed to present the differential diagnosis of a manic state in this fashion: "All signs of the classic mania of the manic-depressive psychosis may occur in schizophrenia, but a manic who shows marked schizophrenic traits is not a manic manic-depressive but a schizophrenic." The principle in general medicine that in a combination of two diseases, a minor one and a major one, the major one is diagnosed is not the only reason for this point of view. The main reason is the direct observation that the cases with a combination of manic and marked schizophrenic signs usually develop later into a classic schizophrenia, and often a very severe schizophrenia. However, there are some cases which suggest a combination of both diseases, on clinical and hereditary grounds and by reason of the further course of the disease. Space does not permit me to go into these now. In the following paragraphs I shall enumerate some criteria by which we in Burghölzli determine schizophrenia, since in America the procedure of differential diagnosis is different.

There are many ways in which the basic schizophrenic disorder may become evident in manic states. When the manic manic-depressive patient becomes aggressive his whole person is filled with anger. Usually, he gives clearly the reasons for his anger. Not so the schizophrenic patient in the manic state. He becomes violent quite unexpectedly and without apparent reason. We do not feel his

anger even when he speaks of it, because his features and his movements are not in agreement with his words. He may strike us with the most friendly smile on his face. In brief, his actions are unintelligible to us, until we study the schizophrenic unconscious mechanisms, whereas even an attendant is able to perceive the causes of a manic patient's excitement. The manic patient acts with his whole being, while the actions of the schizophrenic patient are determined by only a part of his personality, which explains the differences described.

I recall a patient who was in constant motion and therefore, superficially, seemed to be manic. She would go frequently to the window, touch it or look out of it, and then try violently to force the door. These actions were unintelligible because when the door was left open she made no move to escape. She herself could give no reasons for her behavior. A further study of the case revealed that the psychosis became evident when the patient repeatedly entered the room of a youth who lived in the apartment in which she was employed. When he finally had to lock his door, she tried to enter by force. This behavior was responsible for her being in the hospital, and she constantly rehearsed this scene in her psychosis. She had identified her lover with the gardener in her unconscious, and felt in touch with him if she merely looked through the window at the garden, and, eventually, if she merely touched the window. These are all schizophrenic mechanisms. When a real manic patient looks out of the window, it is because he is greatly interested in something outside, and when he has a violent urge to force himself out of the door he can readily explain his plans for the outside.

According to our records at Burghölzli, the schizophrenic patient in a manic state lacks effective rapport. The real manic patient tries to get in touch with us and wants to interest us, while the schizophrenic patient may carry on his activities without even noticing the physician. I recall a patient who frequently interrupted her knitting to get up and turn somersaults. When the stocking was finished there were no dropped stitches or other mistakes. Only a part of her personality compelled her to turn somersaults, while another part was calm enough to allow her to knit stockings perfectly.

As has been emphasized here by Dr. Jameison and Dr. Sprague, the flight of ideas may resemble in part the schizophrenic disorder in association. Indeed, alliterations and mediate associations lose their diagnostic value altogether in the manic states. On the other hand, when they occur in a depressive state they are suggestive of schizophrenia. There are other dissociative disorders which are particularly clear schizophrenic signs when they occur in the manic states: short associations, deprivation of ideas, blockings and having nothing to say.

However, in practice, there are means by which the schizophrenic associative disorders can be differentiated from a mere manic flight of ideas. In a manic patient one may expect a proportionate relationship between associative disorder and elation. The more elated the patient, the more dissociated are his ideas. In a schizophrenic patient, there may be a very great dissociative disorder accompanied by a very slight elation. If one receives an extremely dissociated letter in exquisite form and handwriting, one may conclude that it comes from a schizophrenic person in whom different functions are affected in different degrees.

Delusions and hallucinations may occur in manic as well as in schizophrenic patients. For instance, a manic patient may think not only that he is the best worker in his group, but that he has a great deal of political influence as well. But these delusions must correspond in intensity to the flight of ideas and elation. A patient who discusses a mathematical problem intelligently and at the same time maintains that he leads the meetings of the League of Nations by wireless telegraphy has schizophrenia. Here, obviously, an isolated mechanism which produces a delusion of grandeur is altogether separate from that part of the personality which is calm enough to discuss the mathematical problem. A real manic patient may hear the voice of God praising him, but the content of his hallucination is in direct connection with his mood. Irrelevant hallucinations, or voices that call the patient a sinner while he is in an elated state, are characteristic of a schizophrenic state. The same holds true for hallucinations and delusions that persist after a change of mood.

My father would be in entire agreement with Dr. Russell about the difficulty of diagnosis in acute confused states. Until it can be proved that the patient's perception of his environment is complete, every sign that ordinarily would be clearly schizophrenic has no diagnostic value. Confused states, with difficulty in perception and lack of understanding of the environment, may produce a picture containing definite schizophrenic symptoms. In such states the differential diagnostic examination must show that the patient's difficulties in perception and in grasp of his environment are not the primary disorder, if the diagnosis of schizophrenia is made. A patient's understanding of his environment may be often quite unexpectedly revealed by a sudden and chance remark. Or all at once he may follow a complicated order, or prove his understanding of it by doing just the opposite. For example, when asked to tell what two times four is, he may give every number from one to ten except eight.

Influenzal delirium has often been mistaken for the acute confused states of schizophrenia, and such states also occur in the toxemia of

pregnancy. But in these cases, in addition to the mental illness, severe physical symptoms are also found, such as a blood picture like that in pernicious anemia, icterus or eclamptic attacks. So-called pregnancy and postpartum psychoses without physical signs, but with marked schizophrenic features, that have been observed in our clinic have turned out to be real schizophrenias. We have always been cautious in Burghölzli about diagnosing toxic psychoses without pronounced physical signs. Atropine deliriums, tumors of the brain, uremia and very often the twilight states of epilepsy will also produce the picture of a confused schizophrenic condition.

I do not consider it necessary to discuss my father's point of view of the differential diagnosis between schizophrenia and other mental diseases, since he applies the same principles that I have tried to summarize here in the differential diagnosis between schizophrenia and the manic-depressive psychosis.

PROGNOSIS

I shall proceed now to the matter of prognosis. Since I have already discussed the outlook for the disease in general, I shall mention briefly only a few points which my father has particularly emphasized. According to his chief prognostic principle, the outlook becomes worse: (1) the more advanced the primary schizophrenic disorders, and (2) the clearer the mental state in which they are observed.

Manic and depressive episodes, confusion and excitement are altogether temporary and pass away. When a greater part of a condition is due to them, its prognosis is good. The prognostic (and diagnostic) significance of a schizophrenic sign is much more marked when it has been observed in a calm state rather than in an emotional state. On the other hand, the matter of intellectual insight does not seem to us at Burghölzli to be a matter of great prognostic importance. Because of the splitting of the psychic functions, schizophrenic patients frequently have strikingly good insight. A part of the mind watches objectively the pathologic phenomena caused by another part. Even patients in advanced cases may tell us that their ideas are delusions and hallucinations. But this does not make the outlook for the future more hopeful. On the contrary, we find a great lack of intellectual insight in many patients who do well. An affective insight is more important.

As a rule, we believe that catatonic signs in acute and excited cases have no serious significance. Yet we do not believe that the prognosis in other forms of schizophrenia is markedly worse. In fact, we believe that the beginning catatonias with a chronic onset of catatonic signs in a clear and calm state have the worst prognoses.

Through the study of a large number of cases, my father has shown that a good remission after an earlier episode generally warrants the expectation of another extensive improvement. He agrees with Kretschmer and Gaupp that the cases in patients with a pyknic somatic habitus frequently have a better prognosis. Often these cases of schizophrenia follow a cyclic course. It is striking how the pyknic patients preserve their affective touch with other people, even when they deteriorate. And finally, my father believes that the prognosis depends to a certain extent, after all, on therapy.

THERAPY

It has interested me that the therapeutic principles used in our clinic are very similar to those I have observed in this country and particularly in this hospital. As a matter of fact, they are much more similar than the theoretical conceptions. This may indicate that the theoretical differences are perhaps differences of terminology rather than of fact.

My father's attitude toward therapy is definitely optimistic, though he points out that to date nothing has been found to influence the primary process. As I have tried to indicate, however, he regards as secondary most of the symptoms that make a schizophrenic patient a sick person in the social sense. He does not believe that it is possible to keep a schizophrenic patient from being a rather peculiar and original individual, who presents definite pathologic manifestations in the psychologic tests as long as he lives. But he does believe it is possible, even with limited knowledge, to prevent a schizophrenic patient from being a violent, untidy inhabitant of an isolated room as long as he lives. Likewise, he believes it possible to bring a large number of schizophrenic patients to a fair social adaptation, some of them as chronic patients of the better wards of institutions, but a majority as individuals living and working outside of hospitals. This optimistic attitude is due not only to individual observation of thousands of patients, but to comparison between hospitals in which schizophrenic patients were treated and hospitals in which they were not.

My father has been very critical of the use of many recommended therapeutic measures in schizophrenia. He always considers the possibility of apparent cures being really spontaneous remissions. He has studied various methods, such as cold water therapy and many medical treatments that at one time were popular all over Europe, and found them useless. In fact, he has dealt with them in a rather critical fashion in a special chapter of his book "Autistic Thinking in Medicine."[1] He has come to the conclusion that with our knowledge to date, the only

1. Bleuler, Eugen: Das autistisch-undisziplinierte Denken in der Medizin und seine Überwindung, ed. 4, Berlin, Julius Springer, 1927.

effective therapy in schizophrenia, apart from a few symptomologic measures, is of psychic character. He attributes all the success of the therapeutic measures which I have mentioned to psychic influences. This attitude was severely criticized fifteen or twenty years ago.

The general trend of my father's psychotherapy has been not to leave the patient alone with his autistic tendencies, but to study him, and prevent him from losing touch entirely with his environment. My father aims to discover what tendencies exist which can be utilized for active connection with the environment, and when they appear. He believes it important to recognize the passing of the acute schizophrenic episode, for at that time the patient may retain his pathologic behavior just because there is no incentive to discard it. He has cited frequent examples of the difficulties facing a patient who has been excited, noisy and untidy on a disturbed hall, when he must find his way back to calm and reasonable living. The problem is serious enough if he has a normal mind and not a schizophrenic one. Klaesi has published some illustrations of sudden psychologic action on the part of the physician which has had the immediate effect of ending seriously disturbed behavior. For example, by offering his clean handkerchief to a violent and untidy occupant of an isolation room he brought about an essential change for the better in her case. This act made her realize that she was once more in contact with cultivated people, and that her delusional ideas were no longer true.

My father is of the opinion that psychoanalysis has no direct effect on schizophrenic patients, and on this point he is in agreement with most psychoanalysts. But he thinks highly of the indirect influence of psychoanalysis on schizophrenic therapy—on account of the contribution of psychoanalysis to the understanding of the disease in general and of the peculiarities of individual cases in particular.

I lack space to go into details of the therapy that is applied at Burghölzli. Occupational therapy and the entertainment of patients in their free time play an important rôle, of course. I shall select only three procedures that are given particular consideration there, namely, the early discharges, the family care of schizophrenic patients and the sleeping cures.

When many schizophrenic patients come to the hospital, their acute episode is over, and direct psychic influence has no further effect on them. They begin to stabilize their peculiarities, and to adapt themselves completely to hospital care. Quite sudden discharges after a brief period in the hospital, even of some patients who seemed unequal to life outside an institution, bring many encouraging results. For this reason my father is much inclined to try discharges in these cases. Some of these patients come back the same day or the next, but others

are often able to remain outside and to work for months or years. We are inclined to believe that this procedure is a means of saving many patients from chronic hospitalization. It is made easier by the fact that in Switzerland we do not have regular court commitments to mental hospitals.

These sudden discharges are only one kind of general environmental change that has been found useful. Transfers from one ward to another and from one hospital to another often bring beneficial results. It is an important task of the physician to recognize the moment when the patient is ripe for a change.

Family care of schizophrenic patients has been organized and directed by Klaesi and Staehelin in the Canton of Zurich. It proved to be not only a good and inexpensive care, but also a frequently important psychotherapeutic measure for the patient. By a careful choice of environment many of the complexes of the patients may be either avoided or satisfied. For instance, one patient may not get along at home because she is jealous of her married sister with whom she lives. Or another may feel inferior because his work is on a lower social scale than that of his brothers. This feeling of inferiority may hinder him from adjusting socially to his brothers' environment. He may enjoy consoling himself with the idea that his health necessitates working on a farm. A family in the country can offer him this very opportunity. A patient with a superiority complex who comes from the country may be happy to live with and be cared for by a cultivated family in a city. For certain patients work can be found, such as mechanics, which fully satisfies them and keeps them outside of institutions.

Families are often selected because one of their members has formerly been a nurse in a hospital. Their qualifications are well known, and a choice of a particular family environment can be made to suit the patient's personality. Many patients have an opportunity to earn a portion of their living by doing satisfactory work. Some of them remain with their nursing families; for others this foster-home is a step toward independent living later on.

Sleeping cures were instituted by Klaesi. Hypnotics are administered so that the patients sleep almost constantly, awaking only for feeding and voiding. Usually, the sleep should last from a week to ten days. There is an element of danger in the sleeping cure, but this element becomes very slight under extremely attentive care of the physician and the nurse. The patient's physical functions, especially his diuresis, his respiratory organs and his pulse, must be constantly watched. It is of the greatest importance that no more of the hypnotic be administered than is absolutely essential for a quiet

sleep. This means that the nurse must call a physician at any time, day or night, when the patient begins to awaken. It would be a grave mistake to give a patient who is still asleep a dosage sufficient to ensure sleep all night. By waiting until the sleep is finished, the physician may be able to use less hypnotics. Of course, the cure must be interrupted immediately if diuresis becomes severe, if the patient ceases to expectorate or if any other of his somatic functions becomes disordered. There is a choice of several hypnotics for these cures. We usually start the sleep with one dose of scopolamine morphine, and a dose of 4 cc. of a derivative of allyl-isopropyl barbituric acid, administered intramuscularly, or a dose of 0.4 Gm. of sodium phenobarbital may follow. The additional doses have to be determined by the patient's weight, sex, general physical condition and, particularly, the depth of his sleep and his individual sensitiveness to the hypnotic. Therefore, no rule can be given.

The effect of the sleeping cure is purely psychologic, just as are all other therapeutic measures in schizophrenia. Its purpose is to prevent the schizophrenic peculiarities from becoming fixed, and to give the patient the chance and the motive for a new and better adaptation. Therefore, the psychologic treatment, which must begin at the moment of awakening, is of the greatest importance. Now the physician strives to interest the patient in his surroundings and to get in touch with him. The sleeping cures are indicated, naturally, in only a small number of cases; namely, when the patient does not improve in his behavior after an acute episode, in spite of the absence both of acute signs and of signs of deterioration. For example, if an excited patient continues to be violent while showing less fear, less confusion, few hallucinations of sound (especially of shooting) and occasionally good affective rapport, one may conclude that a sleeping cure is liable to stop his violence and render him accessible to direct psychotherapy.

COMMENT

If I were to express briefly what I have said about my father's conception of schizophrenia, it would be this: He has a great tendency to sympathize with the schizophrenic patients and to share their fears and their worries. He is happy when he feels that something in a schizophrenic patient's mind responds to his attention. I believe that all his conceptions about schizophrenia have been due directly to this attitude. Both the basis and the result of his work with schizophrenic patients have been the conviction that it is worth while to give them individual interest and personal sympathy.

Bloomingdale Hospital.

Abstracts from Current Literature

THE PATHOLOGIC ANATOMY OF CHRONIC ALCOHOLISM. T. OHKUMA, Ztschr. f. d. ges. Neurol. u. Psychiat. **126**:94, 1930.

While the symptomatology of chronic alcoholism has been carefully studied, research on the pathology of this condition has not kept pace with the clinical studies, because careful investigations of the central nervous system in toto have not been carried out. Ohkuma reports several cases of chronic alcoholism with careful histologic studies. In his first case there was a clinical picture of delirium tremens. Histologically, there was a diffuse parenchymatous degeneration that was more pronounced in some areas than in others. The changes in the ganglion cells were manifested by sclerosis and fatty degeneration. Though the pronounced astrocytic proliferation indicated a marked reparative tendency, numerous giant glia cells and microglial proliferation indicated that the entire process was not only chronic, but progressive. The vascular system played no important rôle in the picture, except for some adventitial proliferation and endothelial degeneration which could not explain the pathologic condition. The corpora mamillaria were most affected; next, the wall of the third ventricle. The cortex and the striatum were the seat of severe changes, most particularly the precentral convolution, though the process in the cortex was diffuse. The three lower layers of the cortex were most affected, just as in the spastic pseudosclerosis of Jakob and in chronic progressive chorea. The anterior thalamic nucleus and the quadrigeminal region showed marked proliferation of glia fibers and loss of cells. The cerebellum showed a diffuse and focal loss of cells. The changes are like those in eclampsia except that the localization and the tempo of the development of the process are different. It resembles most closely in its histologic picture the spastic pseudosclerosis of Jakob. Here there is a severe, progressive, parenchymatous degeneration with astrocytic proliferation in the gray territories of the brain, especially the centralis anterior, the frontal region, the striatum and certain regions of the thalamus. Here the lowermost layers of the cortex are involved, as in this case. Nevertheless, there are no changes in the corpora mamillaria or in the walls of the third ventricle, and in this respect the two processes differ greatly. Nevertheless, the similarity between this disease and chronic alcoholism is striking, and suggests that spastic pseudosclerosis may be due to a toxic cause.

In the second case, Ohkuma reports a classic example of Korsakoff's psychosis. Histologically, the focal nature of the process was most important. These focal changes were of two sorts: (1) Acute parenchymatous degeneration, with pronounced involvement of the vascular apparatus, and the formation of gitter cells. This was seen most markedly in the corpora mamillaria, which showed a complete loss of ganglion cells and an invasion with gitter cells or astrocytes. In addition, there were the formation of new vessels and endarteritic proliferation. In areas where the changes were not so marked, around the aqueduct for example, the vascular changes were pronounced—proliferation of elements of the vessel walls and vessel sprouting. In addition, there were regressive changes in smaller vessels, i. e., fatty degeneration and swelling of the endothelium. The glia reacted by proliferation of giant cells and of microglia. (2) Focal astrocytic proliferation, with the formation of glial scars. The focal changes are secondary to the vascular pathologic changes.

In another case of Korsakoff's psychosis, the histologic changes represented a transition between the two cases previously described. There were diffuse parenchymatous degeneration, with its chief localization in the cortex, and focal changes of a mild degree in the corpora mamillaria and periaqueductal gray matter.

In a case of delirium tremens there were hemorrhages in the frontal lobe. These were large. The other histologic changes were similar to those reported in the first case.

Ohkuma states that the histologic process in chronic alcoholism, judging by his four cases, is a diffuse, chronic, progressive, parenchymatous degeneration involving a large part of the nervous system. This chronic progressive degeneration may have acute or subacute exacerbations. In addition, there is a focal parenchymatous degeneration in the mamillary bodies and periaqueductal gray matter. The glial reaction in these areas is typical. The vascular reaction is marked, especially in the focal areas, and there can be no doubt that the vascular changes are responsible for the pathologic condition in these focal areas. The vascular changes consist of proliferation and degeneration and proliferative changes in the vessels. The hemorrhages that were at first considered pathognomonic of chronic alcoholism are not an important part of the picture. Ohkuma found hemorrhages in all his cases, but they were not in striking localizations, nor were they numerous enough to be of value. Moreover, they always seemed to be recent.

The entire process in chronic alcoholism is toxic. Is one justified in attributing this to the alcohol? That alcohol has an effect is not to be denied, because it can be recovered in the blood and the spinal fluid of patients with acute alcoholism. Korsakoff himself, however, recognized that the symptoms do not always develop in relation to the alcoholism, and there are many who believe, therefore, that chronic alcoholism is caused not by the alcohol but by poisons formed elsewhere in the body. The alcohol reaches the nervous system by means of the spinal fluid. The relation of the changes in the corpora mamillaria and periaqueductal gray matter is not clear.

Ohkuma believes that a hard and fast differentiation between the various clinical forms of chronic alcoholism is not possible. From an anatomic standpoint this cannot be made. The anatomic process is the same in all cases, but the difference is one of intensity.

ALPERS, Philadelphia.

FREUD'S THEORY OF INSTINCT AND OTHER PSYCHO-BIOLOGICAL THEORIES. L. S. PENROSE, Internat. J. Psycho-Analysis **12**:87 (Jan.) 1931.

The writer of this paper criticizes the recent attempts by psychoanalysis to extend the application of some of Freud's theories and to establish an identity with similar theories and laws that have been evolved in the physical and the biologic sciences.

"One of the most difficult though most important studies in the domain of psycho-analysis is the investigation of the relation of the pleasure-pain principle to instinct." Freud introduced dynamic factors into psychology. The study of processes and their mutual reactions, rather than states, enabled him to form a conception of unconscious mental activity, and these processes, he stated, were the older primary processes of the mind and were governed entirely by the pleasure-pain principle. In certain conscious processes, another principle became operative —the reality principle—according to which the mind accepts that which is real even though it is unpleasant. This led to the grouping of instincts under two headings: (1) ego, or self-preservative instincts, and (2) libido or sexual instincts. The latter remained throughout their development under the domination of the pleasure-pain principle, but the ego instincts gradually replaced the pleasure-pain principle by a modification in which gratification was postponed, and a certain degree of pain was endured to meet the demands of the outer world.

The next theoretical step was to link the pleasure-pain principle with Fechner's principles of stability. Fechner described four states: (1) absolute stability, a continuous state of rest; (2) complete stability, a condition in which, although movement takes place among the particles or masses of a system, these movements continually lead back to the same initial configuration in equal intervals of time; (3) approximate stability, in which a condition approximating complete stability is attained, and (4) absolute instability, a condition in which the particles or masses continue to be scattered indefinitely. Freud found the relation to be one between pleasure and stability, and between pain and instability If the mental apparatus could not be freed entirely from excitation, the disturbance was kept at a low or

constant level. This concession enabled the reality-principle to be brought into line with the pleasure-pain principle, which maintains that the seeking of pleasure and the avoiding of pain are the mainsprings of action.

Bernfeld and Feitelberg have recently attempted to show that the principle of stability as applied to psychologic and biologic events is the same as a similar law governing physical events — the second law of thermodynamics. "This law states that, on the whole, in the physical world unstable conditions tend to become more stable in the course of time." This can be no more than a vague analogy, unless instinctual energy is found to be a form of physical energy. Mental energy in Freud's sense is not measurable, and although Bernfeld and Feitelberg claim to show some measurable quantitative changes by differences in temperature, their actual experiments are not convincing. Certain properties of living matter and the complexity of biologic phenomena make the application of these physical laws to psychobiologic events more apparent than real.

In "Beyond the Pleasure Principle," Freud came to the conclusion that instincts, instead of impelling toward change, as one is accustomed to believe, show a conservative tendency expressed in an attempt to bring about the reinstatement of an earlier condition. Ultimately, this repetitive instinctual urge leads back to an inorganic state, which preceded life, and becomes identical with death. Following this lead, Ferenczi ("Versuch einer Genitaltheorie") extended the application of this repetitive compulsion in a scheme for unifying biologic and psychologic concepts of instinct. He saw, for example, conjugation as the reverse of fission, and the sexual act as the reverse of birth. This description of fundamental principles in terms of repetition of events has the advantage that it avoids the complications involved in borrowing concepts from physical science, and that it stresses the qualitative peculiarity of the changes concerned with pain. These are considered to be more important than the quantitative factors.

Can a useful principle of stability which will account for the behavior of living organisms be formulated? Freud's formulations are usually expressed in terms of excitation, but the death instinct is concerned with repetition. A unification of these psychologic and biologic conceptions must link up excitation with repetition. Such a concept seems to be implied in Fechner's definition of complete stability. While a meaning can then be given to the death instinct, it becomes an abstract conception of little practical interest. Present formulations must be regarded as tentative. There are grave objections to formulations in terms of physical concepts. The attempt to show that Freud's death instinct is the same as the second law of thermodynamics is rejected.

GOSSELIN, New York.

NUCLEUS TRIANGULARIS. W. J. GODLOWSKI, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **32**:289 (Oct.) 1930.

The nucleus triangularis is found in all mammals, although it varies considerably in size and structure. Cyto-architectonically three parts are distinguished: (1) a narrow caudal portion consisting of small cells; (2) a mesial portion which contains two groups of cells, one motor and the other the "principal" cells characteristic of the nucleus, and (3) the oral portion which contains only the "principal" cells. The nucleus triangularis is not a part of the nucleus intercalatus. There is no doubt that the "motor" cells of the mesial portion form a direct continuation of the dorsal nucleus of the vagus. Nothing definite, however, can be stated as to its relation to the nucleus fasciculi solitarii.

A careful study of the fiber systems of this nucleus reveals: 1. A dense network of fibers the origin and termination of which cannot be determined. 2. Fibers coming from the area fascicularis and going to the fasciculus Schütz, to the intercalatus and to Roller's nucleus cross transversely the triangularis without terminating in it. 3. Fibers coming from the area fascicularis traverse the triangularis vertically and go mesially or laterally from the fasciculus solitarius to the internal arcuate fibers and to the substantia reticularis, as well as to dorsal and predorsal longitudinal bundles. 4. The striae acusticae and fibers from Deiters'

area and the cerebellum also cross the triangularis more or less horizontally and run toward its midline. 5. Radial fibers which apparently are related to the fasciculus solitarius and to the roots of the glossopharyngeal and intermedius have an almost vertical course. 6. A system of fibers, especially well developed in the oral portion of the triangularis; in some species this system runs as an independent longitudinal bundle. Fibers which run partly through the lateral foot of Schütz's bundle and, partly independent of it, along the margin of the triangularis in the substantia reticulosa, also seem to be connected with this system.

As far as the relations of the triangularis to the area fascicularis and vestibularis are concerned, the fibers of the area fascicularis definitely seem to terminate in the descending portion of the nucleus triangularis. On the other hand, the dense fibers which enter the triangularis proper seem only to cross it without terminating in it. Unfortunately, from a study of Weigert's preparations alone it is impossible to determine whether the delicate fibers of the area fascicularis do not eventually also terminate in the triangularis proper. It is noteworthy that the radial fibers exist exclusively in the triangularis proper and are completely absent in its descending portion.

From a physiologic point of view, Godlowski expresses the belief that in all probability the nucleus triangularis represents a terminal end-station for vestibular fibers. He looks on this structure as one consisting of two different elements, one the "principal" cells and the other the motor cells in the caudal portion. In this sense the "principal" cells may be regarded as sensory elements that have undergone special morphologic differentiation, whereas the other cells belong to the dorsal vagus nucleus and to the intercalatus; i. e., they represent motor vegetative nuclei. In this connection the author also points out that in the present state of knowledge it is impossible to state anything definite about the relationship of the nucleus triangularis to the sense of taste. It is significant, however, that this nucleus reaches its greatest development in *Ungulata, Rodentia,* apes and man; in all of these it is a structure of considerable size. It is very small, however, in *Cetacea,* in which the triangularis as well as the intercalatus are poorly developed. It is also relatively small in the elephant and in *Echidna.* The development of the triangularis runs parallel to that of the intercalatus. These nuclei are closely related to each other. Studies in the Wiener Neurologischen Institute have shown that the intercalatus is a nucleus subserving vegetative nutritional functions. When one bears in mind how important for these functions are the stimuli that are mediated by the intermedius and glossopharyngeus, the correlation becomes obvious.

KESCHNER, New York.

INVESTIGATION ON THE ORIGIN OF EARLY HYPERTONIA AND OF THE NECK REFLEXES OF MAGNUS AND DEKLEYN. V. M. BUSCAINO, Riv. di pat. nerv. **36**:335 (Sept.-Oct.) 1930.

The author investigates the occurrence of very early stages of hypertonia following lesions of the brain and independent from involvement of the pyramidal tract. He also reviews old cases in the literature in which, associated with an early appearance of hypertonia, the reflexes of Magnus and DeKleyn were present. He divides these cases into those in which the pons was involved, those in which the mesencephalon was involved, those in which the basal ganglions were involved and those in which the basal ganglions were iespected. To the clinical cases found in the literature, he adds a description of five personal cases in which hemorrhages or softening of the left cerebral hemispheres was present. In two of the cases, right hemiplegia and hypotonia were present; in one, right hemiplegia was present with hypertonia in flexion at the elbow and at the knee; in another, right hemiplegia was present with hypertonia in extension, and in the fifth, right hemiplegia was present with hypertonia in flexion at the elbow and hypertonia in extension at the knee.

From a review of the literature and from his own contributions the author feels justified in stating that the early hypertonia occurring in these cases is

not dependent on the nature of the destructive process nor on the extension of the lesion; it is not due either to the interruption of the pyramidal tract nor to its irritation. He also came to the conclusion that contraction is not due to the interruption of the frontopontile tract nor to the interruption of the parietal and temporal pontile tracts. The thalamus does not seem to play an important rôle in the genesis of this hypertonia.

In regard to the corpus striatum, the conclusions of the author are that whenever early hypertonia appears, this condition is due to involvement of the striatum, paleostriatum or neostriatum. If the striatum is respected, the hemiplegia is not accompanied by symptoms of hypertonia. It is possible, however, to find hypotonia even in cases of involvement of the striatum whenever the lesion is such as to isolate the mesencephalon from the upper centers without involving the red nucleus or other cellular structures of the same mesencephalon.

Lesions involving the mesencephalon and especially the substantia nigra may result in the production of hypertonia, and the same occurs in lesions involving the pons. On the basis of the various cases reported, Buscaino has tried to summarize the function of hypertonicity in the various segments of the corpus striatum, mesencephalon and pons, and the practical value of his investigation consists in the fact that the presence of such early hypertonia may help in the diagnosis or localization of a lesion.

In regard to the reflexes of the neck, his investigation concludes for a fact that their appearance is subordinated to lesions of the lenticular nucleus and of the lower pons. The lesions of the pyramidal tract and of the frontal parietal and temporal pontile tracts of the thalamus and of the caudate nucleus are not necessary for the appearance of such reflexes in the neck. However, if the lesions involving the lenticular nucleus are large enough to establish a complete disconnection between this nucleus and the mesencephalon (mesencephalization of Buscaino) the reflexes in the neck may be absent.

FERRARO, New York.

THE STRUCTURE OF NERVE FIBERS. L. JABUREK, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **32**:1 (Oct.) 1930.

Histopathologic examination of swollen nerve fibers shows that swelling of the axis cylinders occurs in two phases. In the first phase, there is purely an increase in the thickness of the axon, and in the second, a marked increase in its length. Swelling of the myelin sheath, however, occurs only in one phase, during which there are a marked increase in its circumference and a lesser increase in its length and thickness. The ratio of swelling (circumference: length: thickness) is approximately as 8:1:1. In the process of swelling, the caliber of the myelin tube is increased to a greater extent than the thickness of the axis cylinder. As a result of this, in very marked swellings of nerve fibers, a circular cleftlike formation occurs between the axis cylinder and the myelin sheath.

The changes in shape and volume of the myelin sheaths and axis cylinders of swollen nerve fibers have all the characteristics of an anisodiametric swelling (a swelling in which the axes are unequal). During the first phase, the axis cylinders swell only in both horizontal axes, and during the second phase in all three axes, whereas the myelin sheaths swell in all three axes. The length of a swollen myelin tube almost approximates its thickness, but its circumference is much greater. The optical properties of the anisodiametric swellings of a myelin sheath correspond to those of the axis cylinder, both mediums being doubly refractive to light.

Jaburek assumes that an anisodiametric swelling depends on the special structural peculiarities of the swelling medium. On the basis of a theoretical principle of angles he would, therefore, construct the following hypotheses: (*a*) The myelin sheath of a nerve fiber consists of myelin fibrillae (myelin plates), which on cross-section of the myelin tube appear as a segmental, striped "spokelike" formation. When the segments of the various spokes run into each other, they form angles that are at the basis of the relationship of the swollen axis cylinders to that of the cross-section of the myelin sheaths (8:1). In longitudinal sections,

the myelin fibrillae make an angle of almost 45 degrees with the axis cylinder. In some areas the fibrillae run parallel, whereas in other areas they run against each other at angles, depending on the "angle principle of swollen spaces." These relationships determine the uniformity of the axial swelling in cross-sections of the myelin sheath (1:1). (*b*) The theoretical description of the structure of the myelin tube is in harmony with the important anatomic structural features of the myelin sheath. This is especially the case with the Schmidt-Lantermann incisures, the Golgi funnels and their spirals, the honeycombed and spokelike structure, the spongy myelin and the neurokeratinous network, all of which are the natural results of the peculiar fibrillary structure embedded in a homogeneous ground substance. (*c*) The axis cylinder of a nerve fiber consists of a bundle of fibrillae which, in the process of severe swelling, break down into granules. These "theoretical" fibrillae may be regarded as identical with the anatomic neurofibrillae, which, in the course of a degenerative process of the axons, also break down into granules. (*d*) Swelling of the nerve fibers is accompanied by alterations in the water content which produce changes in the irritability of the axons. The irritability of the axon is in inverse proportion to its water content.

KESCHNER, New York.

AROMATEMIA AND AROMATURIA FROM TYROSINE IN DEMENTIA PRAECOX. G. G. NOTO, Riv. di pat. nerv. **36**:383 (Sept.-Oct.) 1930.

Inspired by Gullotta's work on the hepatic function in dementia praecox, the author reports the results of his investigation in twenty cases of dementia praecox. The presence of an aromatic substance in the blood was detected by the reaction of Millon, and concomitantly the reaction of Buscaino (black reaction) was tested in the urine. The reaction of Millon was also tested in the urine. In ten of thirteen cases, which did not show a positive Millon reaction before the administration of tyrosine, the reaction became positive. In four cases, the positive reaction present before the administration of tyrosine became more intense. Therefore, fourteen of twenty cases, that is, 70 per cent, showed a positive reaction for aromaturia. Eleven of twenty cases showed concomitant aromatemia and aromaturia, whereas, aromatemia alone was found in three cases and aromaturia alone in three other cases. As controls, the author used a normal person, seven feebleminded persons, one epileptic patient, and one patient who had recovered from a case of mental confusion at the time of the test. In the normal person, the epileptic patient, the patient who had recovered from mental confusion, and five of the seven feebleminded persons, the reaction of Millon in the blood was negative before and after the injection of tyrosine. The reaction of Millon in the urine was negative before the administration of tyrosine in five feebleminded and in one epileptic patient. It was positive in two feebleminded persons and in the patient who had recovered from mental confusion.

The conclusions of the author are that between the controls and the group of patients with dementia praecox, there is a considerable difference in the aromatemia and the aromaturia, as the tyrosine test has established the presence of an aromatic substance in the urine and in the blood of all such patients, whereas, in the controls it was not found in the blood and in only 33 per cent was it found in the urine. The author discusses the significance of the presence of this aromatic substance following an injection of tyrosine, and recalls that an aromatic substance may be derived from tyrosine through a bacterial action. This contention is sustained by Hirai, Sasaki and Stewart. The author, therefore, establishes a connection between his observations and the report in the literature concerning pathologic lesions of the liver and of the gastro-intestinal tract in cases of dementia praecox in order to explain the possibility of the passage through the gastro-intestinal make-up of these abnormal products of the splitting of tyrosine, which are not even utilized by the liver the antitoxic power of which is lowered. The author considers that his data support those of Gullotta concerning the lowered antitoxic function of the liver and those of Buscaino concerning the enteric origin of amentia and dementia praecox.

FERRARO, New York.

PARINAUD'S SYNDROME APPEARING SUDDENLY IN THE COURSE OF PARKINSON'S DISEASE. CONFUSIONAL ATTACKS AND PARADOXICAL KINESIA. H. BARUK and J. DEREUX, Rev. d'oto-neuro-opht. **8**:763 (Dec.) 1930.

Mrs. J., aged 57, suffered an attack of eclampsia at the age of 29. Following this and up to 1923, there were three or four epileptic attacks yearly, which ceased when parkinsonism appeared. Examination revealed a complete parkinsonian syndrome, with retropulsion, trembling, rigidity and cenesthetic disturbances: sensation of the nails being detached and of the body becoming smaller. Under treatment with *Datura stramonium,* the trembling disappeared, but the rigidity became immediately more marked and walking became impossible. When scopolamine was substituted, the rigidity decreased and walking was possible, but the trembling returned. A curious fact was that, shortly before the time for the dose, there was a sensation of dryness of the mouth (usual after large doses of scopolamine) which disappeared as soon as the dose was given.

A few weeks later, Parinaud's syndrome suddenly appeared: paralysis of the movements of raising and lowering the eyes, both voluntary and automaticoreflex. Next there was a marked access of mental confusion, which was followed by ideas of persecution. The anxiety became more intense and one day, with a cry of terror, the patient, who had been confined to bed by the extreme rigidity, bounded out of bed and tried to jump out of the window. Two days later, death occurred.

The following points are emphasized: (1) the disappearance of the epileptic attacks when the parkinsonian syndrome appeared; (2) the alternation of trembling and rigidity; (3) the sudden onset of Parinaud's syndrome, which is not often seen in ordinary Parkinson's disease, although it is frequent in chronic encephalitis. This is one more argument in favor of the theory that Parkinson's disease is not a morbid entity and supports the identity of the seats of the lesions that cause paralysis agitans and the postencephalitic parkinsonian syndrome; (4) the paradoxical kinesia in the course of the confusional attacks. Jarkowski thought that external excitations play an important rôle in its causation. Everything that augments the sum of the perceptions of the patient may increase the activity of the parkinsonism. Psychic factors also play a part.

"The paradoxical kinesia, which we report, and its relation to the confusional crises open up some vistas of the reciprocal perturbations and the interaction of the psychomotor functions on the one hand, and motor and postural automatisms in the course of organic cerebral affections on the other."

DENNIS, Colorado Springs, Colo.

INFLUENCE ON EPILEPSY OF A DIET LOW IN THE PELLAGRA-PREVENTIVE FACTOR. N. P. WALKER and G. A. WHEELER, Pub. Health Rep. **46**:851 (April 10) 1931.

This report which comes from the Milledgeville State Hospital, Georgia, concerns an interesting and unexpected development in the work on pellagra begun by Goldberger a number of years ago at that institution. A patient who had convulsions on an organoneurologic basis acquired pellagra during the third month of treatment with a high fat or ketogenic diet. On the appearance of the pellagra there was a rapid decrease in the number of convulsions, leading to complete freedom from them over a period that lasted for two months and four days, with great improvement also in the neurologic symptoms. The possibility was considered that this favorable result might have been influenced by the shortage of the pellagra-preventive factor, by some other factor in the diet or by the pellagra itself. The pellagra cleared up promptly with a change in diet and the administration of yeast, but after the period of freedom, during the convalescence from pellagra convulsions reappeared and, in somewhat lessened degree than before, have continued for two years.

Further study was made on a group of ten white women whose cases were diagnosed as idiopathic epilepsy, and later on a second group of eight white,

female epileptic patients. These patients were segregated and kept under direct observation at all times during the study. No evidence of pellagra had been observed in any of this group previously during their residence in the institution, and no mention was made of it in their commitment histories. Details of the study and of the diet on which the patients were kept during the period of observation are given, as well as the history and details of the individual patients. All but two patients showed a temporary reduction, amounting to 50 per cent or more, in the number of convulsions at the time pellagra appeared or during its progress. Patients were cured of pellagra at will by the addition of a nitrogen-free, watery extract of yeast or of commercial dry powdered yeast to their diet, and nearly every patient cured of pellagra showed an increase in the number of convulsions to about the average for the individual patient.

Reference is made to the work of Wilder, Peterman, McQuarrie, Greer and Guthrie, and the opinion is offered that whether a deficiency in the antipellagric vitamin is itself a direct factor, or whether, as seems more probable, pellagra, acidosis and dehydration are merely common surface indications of a more specific and profound metabolic change, is a question that cannot be answered from the information at hand.

WILLEY, Albion, N. Y.

INDISTINCT TYPE OF THE CESTAN-CHENAIS BULBAR SYNDROME: PARALYSIS OF THE NINTH, TENTH AND ELEVENTH CRANIAL NERVES AND A SLIGHT LEFT HEMIPARESIS. H. ROGER, A. CRÉMIEUX and Y. POURSINES, Rev. d'oto-neuro-opht. **9**:89 (Feb.) 1931.

A man, aged 52, entered the clinic with a history of headache in the right temporoparietal region, pain around and in the right ear, difficult deglutition and regurgitation of liquids through the nose. Several examinations were made, the results of which may be summarized. There were: paralysis of the ninth, tenth and eleventh nerves on the right, with a slight involvement of the fifth and seventh and exophthalmos of the right eye; a slight hemiparesis and hypotonus, more marked in the left leg; a bilateral Babinski sign; hemihypesthesia to pricking on the left, with conservation of thermic sensibility; hypesthesia in the zone of Ramsay Hunt on the right; atrophy of the hands, especially of the left thenar eminence. The Bordet-Wassermann test of the blood gave negative results.

Two questions arose: 1. What was the seat of the lesion? 2. What was its anatomy and etiology?

The involvement of the right glossopharyngeal, pneumogastric and spinal accessory nerves, associated with a left pyramidal syndrome, warrants a localization in the right side of the spinal bulb. This syndrome approaches the syndrome of Cestan-Chenais, which consists of: on the side of the lesion, hemianesthesia of the face, velopalatolaryngeal hemiplegia, cerebellar hemisyndrome and the syndrome of Claude Bernard-Horner; on the opposite side, hemiparesis of the limbs and a hemianesthesia of the syringomyelic type. The case reported differs in that the pyramidal bundle is affected on both sides, exophthalmos replaces the Claude Bernard-Horner syndrome, the cerebellar syndrome is not distinct, the crossed hemianesthesia includes touch and pricking, but not temperature, and there is atrophy of the thenar and hypothenar eminences, which is especially marked on the left.

Bulbar neoplasm, amyotrophic lateral sclerosis and poliobulbitis could be ruled out. The relatively sudden onset, the clear systematization of the lesion to one side of the bulb and the grouping of the symptoms which suggests the syndrome of Cestan-Chenais point to a vascular lesion — thrombosis of the lateral artery of the bulb. The amyotrophy of the hands and the homolateral Babinski sign may be explained by atheroma of the collaterals of the anterior spinal artery, causing swelling of the cervical medulla. Syphilis is one of the chief causes of bulbar softening and, in spite of the negative history and the negative results of the Wassermann test, a therapeutic test is indicated.

DENNIS, Colorado Springs, Colo.

HALLUCINATIONS IN A VISUAL SEMIFIELD FROM SPASM OF THE SYLVIAN ARTERY. M. JANBON and H. VIALLEFONT, Rev. d'oto-neuro-opht. **9**:94 (Feb.) 1931.

The presence of visual hallucinations in a clinical picture of intracranial hypertension points to tumor of the temporal lobe. A woman, aged 70, with signs of arterial hypertension, complained of bilateral headaches, cramps in the legs, nocturnal pollakiuria, dyspnea on exertion and occasional anginal sensations. Periods of amnesia, disorientation, vertigo and aphasia had existed since the age of 53. Aphasia occurred especially in the mornings on rising from a recumbent position or after fatigue, and was accompanied by pains in the back and difficulty in moving the right hand. Latterly, visual disturbances had appeared; the patient would see bouquets of red, blue, green or yellow roses in the right visual field, and they moved from left to right. She was perfectly aware that the bouquets did not exist and her psychic state was normal. The eyes were normal, except for a slight anisocoria, lenticular opacities, loss of pupillary reflexes to light and in accommodation and slight retinal edema. Arterial tension was variable and unstable, averaging 16 systolic and 9 diastolic, Vaquez.

A critical review of the literature is given. The spasmodic character of the hallucinations in a patient with hypertension, with no organic lesion of the nervous system, and the appearance of the hallucinations after effort form a typical picture of intermittent encephalic claudication. The motor aphasia, paresis of the right arm and hallucinations in the right visual field identify the trouble as a spasm of the posterior branches of the left sylvian artery. Spasm of the anterior cerebral artery would not cause visual difficulty; spasm of the anterior choroidal artery would cause more important motor and sensory troubles and not aphasia; spasm of the posterior cerebral artery would not induce motor aphasia or paresis of the arm.

The images were colored and of changing colors. It seems that stimulation of the optic radiations by ischemia can provoke colored vision. No other such case has been reported.

Opinions vary as to the seat of the lesion in cases of visual hallucination; the occipital and temporal lobes, optic tract, chiasm, optic nerve and even the globe have all been suspected. Elementary hallucinations are more frequent than true hallucinations and are found especially in connection with occipital lesions.

DENNIS, Colorado Springs, Colo.

THE RELATION OF THE PARANASAL SINUSES TO OCULAR DISORDERS, ESPECIALLY TO RETROBULBAR NEURITIS. S. R. GIFFORD, Arch. Ophth. **5**:276 (Feb.) 1931.

This article is an ophthalmologic review of the literature. In the first part of the paper, the cases presented by various authors are analyzed from one standpoint alone: Were the ocular disturbances caused by disease of the paranasal sinuses or was the etiologic factor an entirely different causative agent? The second part of the review is a discussion of the pathology of the type of retrobulbar neuritis that is caused by disease of the sinuses: the acuteness or the severity of the morbid process; the path of the infection (hematogenous or by contiguity of the tissues); the microscopic changes; the complications that arise, as pneumonia, thrombosis of the cavernous sinus, etc., and the importance of a histologic examination of the bone in disease of the nasal accessory sinuses.

The third part of the review deals with the indications for operation. When one considers the surgical treatment for retrobulbar neuritis one must of necessity eliminate all probable causes other than disease of the sinuses, especially multiple sclerosis, tumor of the brain and amblyopia due to tobacco or alcohol. Only cases can be included in which definite purulent sinusitis is present. The time for surgical intervention, the preoperative treatment and the operative results are discussed. The author calls attention to the importance of field studies in determining the advisability of and the time for operation.

In the summary of the article, the author again emphasizes the facts that 50 per cent of cases of retrobulbar neuritis are due to multiple sclerosis, that purulent

sinusitis is responsible for about 3.5 per cent of cases, and that in from 15 to 20 per cent of the cases in which no cause can be found opinions still differ as to how many are due to latent or hyperplastic sinusitis. Pathologic evidence seems to show that retrobulbar neuritis may be caused by direct extension. Before operation on the sinuses, every effort should be made to eliminate all other probable causes for the ocular disorder. It is only in this way that accurate statistics can be obtained. The author advises, furthermore, that all tissue removed from the nose be examined histologically. Through a knowledge of the pathology of the morbid process in such cases a better understanding of the whole problem will be obtained. He believes also that there are a number of cases in which exploratory operations on the sinuses are indicated.

SPAETH, Philadelphia.

A CLINICAL AND PATHOLOGICAL STUDY OF TWO CASES OF OBSTRUCTION OF THE AQUEDUCT OF SYLVIUS. SAMUEL T. ORTON, Bull. Neurol. Inst., New York **1**:72, 1931.

The author presents two cases in which a practically complete closure of the aqueduct of Sylvius produced considerable difficulty in the differential diagnosis between obstruction of the aqueduct and expanding lesion of the posterior fossa or of the suprasellar region. Case 1 was that of a girl, aged 17, with a history of slowly progressive mental and physical change during a period of three years. During the first year she showed a slowly progressing degree of apathy and dulness; during the second year she gained rapidly in weight, while an excessive appetite, a desire for sweets and polyuria developed. The latest symptoms to develop were unsteady gait, with a wide foot-base, and definite signs of involvement of the pyramidal tract, which were greatest on the left side. The diagnosis of a pituitary tumor had been made before admission to the hospital. A ventriculogram showed that the lateral ventricles were markedly dilated, but not deformed or displaced. The patient died on the eighth day after the ventriculography; histologic study showed that the aqueduct of Sylvius was blocked as the result of granular ependymitis.

Case 2 was that of a boy, aged 9, whose symptoms appeared only three months before admission to the hospital. The first symptoms were enuresis and polyuria; then a rapid gain in weight and impairment of vision appeared. Because of the pituitary syndrome and roentgen changes in the region of the sella, an operation was performed, and a postchiasmal mass of bluish membrane found. On opening this, clear fluid, under pressure, escaped. Fluid drained intermittently from the wound; the patient died four weeks after the operation. Histologic study showed an occlusion of the aqueduct of Sylvius due to a small astrocytoma.

The author discusses in some detail theories of the etiology and the effect of increased pressure on the structure of the cells. He believes that a clinical history of mental deterioration and apathy may be of value in interpreting chronic cases of this nature. He thinks that there may be an inherent tendency toward a heavy glial framework in cases in which glial growths appear later, and that enlargement of the head from infancy may indicate a reduced factor of safety in ventricular drainage and may be of value in differentiating stricture of the aqueduct from tumors of the posterior fossa and suprasellar growths.

KUBITSCHEK, St. Louis.

HEREDITARY OPTIC ATROPHY (LEBER'S DISEASE). H. S. KUHN, Arch. Ophth. **5**:408 (March) 1931.

This article is a presentation of a case of hereditary optic atrophy or Leber's disease in a man, aged 25. The same condition had developed in the patient's brother five years before, and two uncles also had probably had the disease. The onset in this case was abrupt, and when the patient first presented himself the pathologic process, though in an early stage, was definitely present. The fields of vision showed bilateral central absolute scotoma with a slight concentric contraction of the field of form, which was definitely more extensive in the left eye.

An exploratory craniotomy was performed. Some tissue that showed chronic arachnoiditis was removed at the time. For a time after the operation vision improved, in the right eye from 20/100 to 20/50, and in the left eye from counting fingers at 12 inches to 9/200. The central scotoma in the left eye decreased in size, and in the right eye it disappeared. Six months after the operation, vision began to fail again, even though the progressive atrophy of the optic nerve had apparently been halted. An encephalogram was made, with complete drainage of the spinal canal, but the air failed to enter any of the ventricles, even though there was apparently no obstruction in the aqueduct of Sylvius. It was assumed that there were adhesions around the fourth ventricle, which had blocked off the usual foramina through which air gains access to the ventricular system. A ventriculogram showed very little ventricular disturbance. The only part of the ventricular system that was not seen was the fourth ventricle. If there was an obstruction to the ventricular system it must have been between the foramina of Magendie and the aqueduct of Sylvius. But this obstruction could not have been great, since there had not been any internal hydrocephalus or signs of intracranial tension. The appearance of the encephalogram was such as one might see after a chronic encephalomyelitis or after a hemorrhage into the subarachnoid space. There were no signs of a pathologic condition near the optic chiasm.

The author closes these clinical and surgical observations by pointing out that in cases of Leber's disease no destructive silent tumorous masses are found to account for the atrophy of the optic nerve; there is no internal hydrocephalus, nor is there any pathologic condition at the chiasm itself which could cause the atrophy.

SPAETH, Philadelphia.

A CASE OF BINASAL HEMIANOPIA. C. DEJEAN, Rev. d'oto-neuro-opht. **9**:28 (Jan.) 1931.

The binasal hemianopias occurring in the course of optic atrophy are accidental and are therefore not discussed.

Binasal hemianopia must be caused by bilateral compression of the chiasm, since the direct fibers are mostly in the lateral parts. In chiasmatic lesions there is not a sharp division into two hemifields, one clear and one clouded. Such a picture is due to a lesion of the cortex or the optic tract. In the chiasm all the fibers, direct and crossed, are grouped in a small space. Here the lesion attacks the direct fibers and then encroaches more or less on the crossed bundles.

A boy, aged 7 years, was seen in February, 1929, with a history of visual trouble since the age of 5. He was obliged to hold an object to one side to see it, and in walking he fell over obstacles in his path. His general health was excellent, except for frequent headaches. At 1 year of age, he suffered from nervous crises — loss of consciousness for from one to five minutes, clamped jaws, purple lips and pale facies; there was no jerking of the limbs, foam on the lips, biting of the tongue or loss of urine. These crises occurred at intervals of one or two weeks over a period of two years. An examination of the fields showed a binasal hemianopia reaching and passing the fixation point. The symmetry of the fields in the two eyes was striking. The media and eyegrounds were normal. The vision for colors was somewhat diminished. The Bordet-Wassermann test of the blood gave negative results. Neurologic and general physical examinations revealed nothing abnormal. A roentgenogram of the skull showed a slight enlargement of the sella turcica.

Binasal hemianopias are rare. Cases due to atheroma of the circle of Willis, meningitic exudate, tabes and tumors of the pituitary body have been reported. Rakowicz said that bilateral compression of the chiasm by a tumor cannot occur, and that binasal hemianopia must be due to a lesion of the eye itself or to a beginning optic atrophy. This may be true of the hemianopias in tabes, but in the case reported there was no nervous symptom or ocular lesion. The headaches and the slight deformity of the sella turcica indicated a chiasmatic lesion. The cause was probably pressure from enlargement of the anterior clinoid process by meningitic fibrosis or by a local osteoperiostitis.

DENNIS, Colorado Springs, Colo.

SENILE PARANOIA. KASIMIR DOMBROWSKY, Jahrb. f. Psychiat. u. Neurol. **47**:171, 1930.

The striking clinical feature of senile paranoia is the absence of general mental symptoms in the presence of a well defined paranoid symptom-complex. In this respect, senile paranoia resembles the paranoia of early life. It would seem also that, although in cases of senile paranoia organic changes may be found in the brain, these have nothing to do with the paranoid symptoms that, in most instances, are based on various forms of hallucinations. Attempts to correlate the clinical features with the pathologic observations in these cases for purposes of nosologic classification also show that the final differentiation between diseases due to senility and those due to arteriosclerosis can be made only anatomically. In the case reported in this contribution, histologic examination showed diffuse atrophy of the cerebral cortex with focal areas of cortical destruction. There was no evidence of inflammation, embolism, thrombosis or softening. The usual changes of senile dementia (senile plaques, Alzheimer's fibrillary disease) were not observed. The process in the cortex was that usually seen in advanced cases of senile dementia. The diffuseness of the lesions made any attempt at localization futile. No topical causal relationship could be established to explain the various hallucinations presented by the patient during life. How far the peripheral sensory symptoms (edema of the legs, trophic changes over the thighs, pruritus of the genitals, etc.) from which the patient suffered were transformed by a diseased brain into hallucinatory phenomena cannot be determined.

The absence of senile plaques in the brain is attributed by the author to complete atrophy of the cortex and marked reduction of its cells. He assumes that the formation of senile plaques bears a certain relationship to the relative integrity of the cortex, i. e., the plaques represent products of cellular degeneration which are due to senile metabolic changes within the cells themselves. When these, however, are destroyed, there is no possibility for the formation of plaques, which can occur only when active metabolic changes are going on within the cells. In this respect the case described represents a type of senile cerebral atrophy that is entirely different from senile dementia; in the former the psychic manifestations are due to disturbances in the elaboration of environmental and somatic impressions by a degenerated cortical apparatus.

KESCHNER, New York.

THE RELATION OF TIME OF DAY, SLEEP AND OTHER FACTORS TO THE INCIDENCE OF EPILEPTIC SEIZURES. FREDERICK L. PATRY, Am. J. Psychiat. **10**:789 (March) 1931.

Thirty-one patients who had a total of 1,013 epileptic seizures in a year were studied by Patry. He groups them as nocturnal, diurnal and mixed. Patients who had more than two thirds of their attacks during the night were classified as nocturnals; those who had twice as many fits during the day as during the night were placed in the diurnal group, while those whose seizures were more evenly distributed were placed in the mixed category. In Patry's series of patients, 45 per cent were diurnal, 20 per cent were nocturnal, and 35 per cent were mixed. This distribution was so similar to the apportionment found by other investigators as to suggest some basic distinction between the patients composing the respective groups.

Many of the physical characteristics were much the same in each group, although Patry attaches importance to small constant differences. He points out that the abuse of alcohol was more common in the mixed than in the diurnal group, although the actual figures are 71 and 63 per cent, a difference of only 8 per cent. He comments on the fact that the duration of postconvulsive confusion was longer in the diurnal group, being sixty-five minutes in one classification and seventy-one in the other — a difference of only six minutes in a characteristic difficult to delimit.

The blood pressure was higher in the nocturnal class, but most of these patients were older than the others. This group, too, is more prone to status epilepticus.

The highest intelligence, the longest interval between attacks and the least deterioration were found in the diurnal class.

On recording the time of day when the attacks occurred, certain concentrations appeared which Patry terms "time peaks." The nocturnal group showed three—10 per cent of the spells occurred between 8 and 9 p. m., 11 per cent between 11 p. m. and midnight, and 9 per cent between 3 and 4 a. m. The diurnal patients showed time peaks between 6 and 7 a. m., 8 and 9 a. m. and 11 a. m. and noon—with about 9 per cent of the seizures at each hour. Patients in the mixed class showed time peaks between 9 and 10 p. m. (10 per cent) and 7 and 8 a. m. (8 per cent).

DAVIDSON, Newark, N. J.

THE MENINGEAL FIBROBLASTOMAS (DURAL ENDOTHELIOMAS, MENINGIOMAS, ARACHNOID FIBROBLASTOMAS). C. A. ELSBERG, Bull. Neurol. Inst., New York **1**:3, 1931.

In the first portion of this paper the author reviews and discusses various explanations that have been offered for the origin of meningeal fibroblastomas; he thinks that the matter is still essentially speculative and calls attention to the need for postmortem studies with special reference to the exact relation of growths to the several meninges. He believes that for such studies meningeal tumors that occur in the spinal membranes are particularly valuable, and that evidence that they do not develop regularly from cells of the arachnoid that have become adherent to or grown into the dura has been obtained. He reviews material from a previous work, which describes tumors definitely growing from the outer surface of the dura without attachment to the arachnoid, and other similar growths attached to either the inner or outer surface of the arachnoid and pia mater. He reviews the embryologic development of tissue that eventually forms these membranes, and suggests that the tumors are growths derived from misplaced mesenchymal cell rests, and that these growths may originate from any of the three membranes. The author's work is based on 100 cases, of which 50 represent cranial, and 50 spinal, tumors. In discussing the gross structure, the author divides the tumors into three groups: (1) hard tumors, firm in consistency and surrounded by a tough capsule; (2) soft tumors with a very thin, limiting capsule and of irregular growth, and (3) tumors with a combination of the hard and soft characteristics. Matters of operative technic are discussed at length, and particular emphasis is placed on the recognition of vascular supply and damage during operative procedure. He states that the bleeding that occurs during the separation of a growth from the pia arachnoid is due mainly to injury to vessels outside the growth. He believes that electrosurgical apparatus is of great assistance in removing these growths. The tendency in the past to attack first the part of the growth furthest away from the midline, because it was first encountered and easiest to free, is undesirable. This should be the last part of the growth to be separated from its bed.

KUBITSCHEK, St. Louis.

HYPERFUNCTION OF THE INFERIOR OBLIQUE. JEAN NORDMANN, Rev. d'oto-neuro-opht. **9**:101 (Feb.) 1931.

As shown in a previous article (*Rev. d'oto-neuro-opht.* **9**:16 [Jan.] 1931), inclination of the head forward and toward the sound side and turning the head to the same side, in paralysis of the superior oblique, relieves that muscle of the necessity for action and avoids diplopia. After a time its antagonist, the inferior oblique, contracts; still later, the paralyzed superior oblique may recover, and this would be manifested by enlargement of the visual field upward and inward, deviation of the globe upward during adduction and diplopia. This is known as hyperfunction of the inferior oblique and has been observed after paresis or paralysis of the superior oblique, following operations on the frontal sinus. Bielschowsky believed that this effect was due to injury of the check ligament of the inferior oblique, which is inserted in the pulley of the superior oblique.

There are also cases of congenital or acquired primary hyperfunction of the inferior oblique, which are not preceded by paralysis of the superior oblique. They are characterized by the same attitude of the head and diplopia as cases of paralysis of the superior oblique, but differ from them in that the diplopia increases with elevation of the gaze and the visual field is enlarged on looking upward and inward. The following is such a case:

A boy, aged 8, whose previous and family history was not significant, was noticed soon after birth to carry his head slightly bent forward and toward the left shoulder. This condition persisted. In this position of the head nothing unusual was noted in the eyes, but on straightening the head the right eye was higher than the left; on looking to the left or with the head on the right shoulder the right eye deviated upward. The right visual field was normal on looking downward and to the left, but was enlarged on looking upward and inward. There was no diplopia. The remedial measure proposed is a myectomy of the inferior oblique.

DENNIS, Colorado Springs, Colo.

STUDIES ON THE PATHOGENESIS OF MULTIPLE SCLEROSIS. RICHARD M. BRICKNER, Bull. Neurol. Inst., New York **1**:105, 1931.

In a former work, the author found that pieces of the spinal cords of rats when immersed in the blood plasma of patients with multiple sclerosis presented a much greater degree of disintegration of myelin than when immersed in the blood plasma of normal persons. The present work is a continuation of study on the pathogenesis of multiple sclerosis in which an effort has been made to determine whether or not the myelinolysis in multiple sclerosis might be due to the activity of an enzyme, and if this were so, whether or not the enzyme might be a lipase. Studies were made on fifty-one patients with multiple sclerosis and on seventy-nine normal persons, as well as on a small group of persons with disease of the nervous system but without evidence of multiple sclerosis. The author gives in detail the procedures employed concerning the changes in the titratable acidity when mixtures of the blood serum or plasma of patients with multiple sclerosis and of control persons were incubated with licithin as a substrate. As a result of the investigation, the author believes that he has found considerable evidence to the effect that an abnormal lipase occurs in the blood of patients with multiple sclerosis. He believes that his observations are not dependent on normal lipasic action on the lipoids of the decomposition of myelin and he does not think that the results are dependent merely on an excessive normal lipase, as the tests indicated a difference in properties between the normal lipolytic agents and those of multiple sclerosis. He also believes that the difference in results between the serum in the plasma of normal persons and that of persons with multiple sclerosis cannot be explained on a basis of simple decreased antilipase activity. It is his opinion that if an abnormal lipase occurs in the blood in multiple sclerosis, proof must also be given that it plays a pathogenic rôle in multiple sclerosis, that it is actually the cause of the destruction of the myelin and not an accidental or secondary product. He assumes that the abnormal lipase described in this report is the same agent as that which produced myelinolysis in the spinal cords of rats in his previous investigation.

KUBITSCHEK, St. Louis.

THE REACTION OF THE MACROGLIA AND THE NERVE ELEMENTS TO EXPERIMENTAL POISONING BY HISTAMINE, GUANIDINE, HYDROCHLORIC ACID, LEAD ACETATE AND THALLIUM ACETATE. C. E. ROBERTI, Rassegna di studi psichiat. **20**:7 (Jan.-Feb.) 1931.

Following the report of Ugurgieri on the reactions of the oligodendroglia and microglia in experimental poisoning, Roberti reports his observations on the reaction of the astrocytes and the nerve cells following various types of experimental poisoning. His conclusions concerning histamine poisoning are that with small doses the nerve cells are only little involved, whereas with massive doses the nerve cells show the so-called severe type of degeneration of Nissl. The reaction

of the neuroglia is very slight. Following poisoning with guanidine, the nerve cells show diffuse severe lesions of the acute type associated with lesions of the neuroglia of a degenerative type. Using hydrochloric acid introduced directly through a cannula into the stomach, Roberti reports lesions located dominantly in the medulla oblongata and pons. Next to the lesions in this area are those in the globus pallidus, the cerebellum and the gray cortex. The lesions are of the regressive type, with acute swelling and vacuolization. There is no tendency of the neuroglia toward proliferative changes, but a diffuse degenerative reaction. Following lead poisoning, Roberti reports diffuse lesions in the nerve cells represented by the severe type of degeneration. The lesions involve also the Purkinje elements of the cerebellum. The astrocytes also show degenerative changes with a tendency toward clasmatodendrosis. Roberti believes that lead has an elective action for the astrocytes. Lead acetate has been used also by Roberti, and the lesions following the administration of from 8 to 11 cg. of the metal in ten or twelve days are located dominantly in cornu ammonis, in the Purkinje elements and in some of the cranial nerve nuclei. The nerve cells show chromatolysis, here and there shrinkage and gradual disintegration. The lesions are not severe or diffuse, and the neuroglia does not seem to participate in the process. Rabbits were used in all of the experiments.

FERRARO, New York.

DISCRETE OCULAR AND LABYRINTHINE SIGNS IN A SUBJECT WITH MENTAL DISTURBANCES. DIRCKS-DILLY, Rev. d'oto-neuro-opht. **9**:85 (Feb.) 1931.

A soldier was brought to the hospital on account of a deranged mental condition. He had collapsed on a street car, and had complained of dizziness and exhibited great anxiety. He then became violent and was forcibly brought in. He soon became calm, but at the sight of some armed soldiers showed great fear and tried to run away. Examination revealed a pulse rate of 60 per minute and a normal temperature. The patient was lying in bed in a state of ecstasy, holding one hand in the air and the head half raised. He responded slowly to questions. He was oriented in space but less so in time and complained of headache and vertigo. The only positive sign of nervous trouble was an occasional epileptoid tremor of the foot when the tendon of achilles was percussed. Bilateral nystagmus, more marked on looking to the right, was present, and tests of the labyrinths revealed hypo-excitability. Visual acuity, with correction, was normal, as were the eye grounds. Diplopia and a paresis of convergence existed. The cerebrospinal fluid was normal; the Wassermann test gave negative results, and the sugar content was increased. Urea in the blood was increased. Several months previous to admission the patient had had a fit of weeping. After a period of imprisonment he had become taciturn, had talked to himself, had had suicidal ideas and woke with difficulty in the mornings. Attacks of somnambulism previously had led to a diagnosis of melancholic depression, with which the author agrees. Hysteria was also considered.

This case belongs to a group characterized by primitive psychic manifestations of epidemic encephalitis. Emphasis is laid on the fact that there exist cases in which the psychic disturbances are so important that one is tempted to consider them pure psychoses but for the fact that physical symptoms of disease of the nervous system indicate an organic lesion. These symptoms are minimal and must be searched for. Cases such as this are baffling, and, in military circles, may be taken for insubordination or simulation. Their organic substratum is in the side of the third ventricle, the place where a subcortical psychic center has been located.

DENNIS, Colorado Springs, Colo.

EXTENSION OF GLIOMA (RETINOBLASTOMA) INTO THE OPTIC NERVE. ALGERNON B. REESE, Arch. Ophth. **5**:269 (Feb.) 1931.

This article is a report of the examination of 119 eyes enucleated for glioma and studied for extra-ocular extension. The series showed that in 52 per cent

of the cases the gliomatous tissue had invaded the optic nerve posterior to the lamina cribrosa. Furthermore, of the 119 cases studied, 43 per cent were doomed to failure before the patient left the operating room, since in the 63 cases in which the gliomatous tissue had invaded the optic nerve posterior to the lamina cribrosa the optic nerve at the time of the enucleation had not been severed distal to the extension of the tumor. The size of the new growth in the globe did not seem to have any bearing on whether or not it extended into the nerve. Extra-ocular extension occurred in only 10 per cent of the eyes enucleated for glioma, and then late and in the presence of an extensive growth. This contrasts markedly to sarcoma of the choroid in which extra-ocular extension is common. In sarcoma, on the other hand, real extension along the optic nerve is extremely rare.

In studying the slides of these 119 cases, Reese calls attention to the fact that the tumorous masses in the optic nerve completely displaced the optic nerve bundles, at times with the size and shape of the bundles surrounded by their septums preserved; the tumorous tissue occupied the site of the nerve fibers. The tumor seems to have but little tendency to invade the fibrous tissue.

As glioma, when fatal, is so usually by extension through the optic nerve and only exceptionally by distal metastasis, the author strongly recommends that as soon as the globe reaches the laboratory, the nerve be severed flush with the sclera and "run through" in forty-eight hours as tissue for biopsy. If gliomatous tissue is then seen extending through the site where the nerve was cut at operation, the surgeon should be notified. He may proceed either with further excision of the nerve, with irradiation or with both procedures.

SPAETH, Philadelphia.

STUTTERING. SMILEY BLANTON, Ment. Hyg. **15**:270 (April) 1931.

Emphasizing the singular importance of speech in both emotional and intellectual development, Blanton warns that no child should leave school with a speech defect. As a matter of fact, between 5 and 10 per cent of high school and college students suffer from feelings of inadequacy or embarrassment in reciting. For the most part, stuttering is a symptom of inability to adjust to the group due to fear, timidity or hate. There is an unconscious inhibition against speech. Blanton reviews the theories of stammering, mentioning the hypothesis of left-handedness, the theory of imagery defect, the supposition that breathing is at fault and the psychoanalytic point of view. An approach by the last technic leads him to believe that in many cases the stammerer is fixed at an oralerotic stage, and for illustration he cites several cases of stutterers who were inordinately fond of their own bodies. In such cases he obtains relief by "retraining the emotions and freeing the libido." Unfortunately, Blanton fails to describe the technic of performing the emotional retraining and libido freeing.

The treatment of stuttering comprises physical and mental hygiene and speech training. Mental hygiene includes the improvement of home discipline, the elimination of rivalry among siblings and the practice of child guidance generally. In school, the stuttering child should be allowed to speak without receiving especial attention because of the speech defect; the danger of other children imitating the stammerer is, Blanton believes, negligible. Speech training includes practice on vowel sounds and training in pitch volume, which he considers of questionable value, and precise phonetic training, which he considers harmful. Practice in speech by means of debates, talks and especially plays and pageants is highly recommended.

As a last word, Blanton warns against asking the stutterer to speak more slowly, to repeat his sentences or to take thought as to how his vocal organs are working.

DAVIDSON, Newark, N. J.

STRUCTURE AND FUNCTION OF THE CELLS OF THE TUBER CINEREUM. UMBERTO POPPI, Riv. di pat. nerv. **36**:397 (Sept.-Oct.) 1930.

The author studied the structure and function of the tuber cinereum and accepts Foix and Nicolesco's division of the cells into the periventricular nucleus, the

nucleus of the optic tract, the accessory nucleus of the optic tract, the ventral nucleus of the tuber and the diffuse parvocellular nucleus formed by small cells that are scattered in the region of the tuber cinereum. Poppi emphasizes the collection of the tigroid substance at the periphery of the cells where there is a corresponding condensation of the neuroreticulum. The cause of such a condensation consists in the presence of a large amount of granules of fat, among which the lipoids dominate. In the cytoplasm of these cells numerous siderophilic granules are found, comparable to the ones found in the suprarenals and in the hypophysis, which in these two glands represent the most advanced stage of the secretion of lipoids. Such granulations in large quantities are especially found in the nucleus paraventricularis. The author insists also on the peculiar character of the nuclei of the cells of the tuber cinereum, which are always vesicular and large and never compressed by fat, as occurs in pigmental degeneration.

Poppi expresses the belief that because of the vascularity of the region of the infundibulum, the endocellular fat must be considered not as a product of disintegration but as a product of integration. He therefore recalls the observations of Abel, Colin and Sato which have proved the presence in the tuber cinereum of an active principle having the biologic property of the principle that is extracted from the posterior and medial and probably also from the anterior lobe of the pituitary glands. The author finally considers and favors the possibility that the cells of the tuber cinerum are elements possessing a secretory capacity in the sense of internal secretion.

FERRARO, New York.

EXOPHTHALMOS ASSOCIATED WITH DIABETES INSIPIDUS AND LARGE DEFECTS IN THE BONES OF THE SKULL. JOHN M. WHEELER, Arch. Ophth. **5**:161 (Feb.) 1931.

This article, together with the one on xanthomatosis or lipoid histiocytosis by Parker Heath which appeared in the *Archives of Ophthalmology* for January, 1931, page 29 (abstr., ARCH. NEUROL. & PSYCHIAT. **25**:1353 [June] 1931), makes a valuable presentation of ocular observations in diffuse liporeticular disease. The combined bibliography of the two articles, although there is some overlapping, is fairly complete. In this article the literature is reviewed extensively. In the former one the ocular observations and the classification of the related syndromes were presented.

The clinical history of a case is given in detail. It covers three admissions of the patient to the hospital. Photographs of the patient and a roentgenogram of the skull showing the wholesale destruction of bone in the orbital region are included. A mass was removed from the child's orbit under ether, which is apparently the first record of the study of material from a living victim of Christian's disease. This mass was fixed, embedded and cut. The microscopic pictures as well as the report are given. The resemblance of this tissue to chordoma is considered.

The article closes with a recapitulation of the symptoms of Christian's syndrome and of the important examinations that are necessary in all cases of unilateral or of bilateral exophthalmos in a child in whom the cause of the exophthalmos is not clearly evident.

SPAETH, Philadelphia.

SOME EFFECTS OF THE INHALATION OF CARBON DIOXIDE AND OXYGEN, AND OF INTRAVENOUS SODIUM AMYTAL ON CERTAIN NEUROPSYCHIATRIC CONDITIONS. H. C. SOLOMON, M. R. KAUFMAN and F. D'ELSEAUX, Am. J. Psychiat. **10**:761 (March) 1931.

Following the suggestions of Lorenz and Loewenhart, Solomon and his colleagues administered carbon dioxide by inhalation to patients in stupors, especially those in catatonic stupors. They found that allowing a patient to inhale 40 per cent carbon dioxide for two minutes would usually bring him out of the stupor, but that the period of lucidity would seldom exceed fifteen minutes. Two patients

with advanced parkinsonism showed at first an increase in the tremor and rigidity when this gaseous mixture was inhaled, but subsequently demonstrated more freedom of movement and less tremor. In the stuporous group, results similar to the effects of the inhalation of carbon dioxide were obtained by the intravenous administration of sodium amytal, although the period of unconsciousness was extended to two hours, and the duration of lucidity to thirty minutes. These observations suggest that the stupor rests on a physiologic level, that it is due to cerebral physiologic changes that are modifiable by the physical and chemical composition of the blood flooding the brain. Solomon and his co-workers postulate that the elevation in activity represents a rebound from the depressing effect of the drug. D'Elseaux breathed a mixture of 20 per cent carbon dioxide with equal parts of nitrogen and oxygen, and became unconscious in two minutes. An examination of his blood during the period of coma showed definite acidosis. On several patients, large doses of histamine were tried without effect.

DAVIDSON, Newark, N. J.

SENSITIVE METHODS FOR THE DETECTION OF BJERRUM AND OTHER SCOTOMAS. C. E. FERREE, G. RAND and L. L. SLOAN, Arch. Ophth. **5**:224 (Feb.) 1931.

The subject of quantitative perimetry is, without doubt, one of the most important in ophthalmology. Furthermore, by reason of the relationship that exists between the fields of vision and neurology an article such as this is of great importance to the neurologist. True, the technic, as given in this article, applies largely to the uncovering of pathologic conditions that are peculiar to the globe of the eye itself. The same methods, however, apply to any form of disease in which perimetry is indicated.

The major portion of the article is given up to minute details of technic. Form stimuli of low visibility are considered, as well as a decrease in the size of the stimulus, a decrease in the difference in the coefficient of reflection between the stimulus and the background and a decrease in the intensity of the illumination. The use of colored stimuli proved to be enormously more effective in the detection of incipient scotomas and of small changes in the advance or the recession of the scotomatous condition. For the effective use of colored stimuli the necessity for a background of gray of the brightness of the color is emphasized.

The subject matter of this extensive article is of the greatest interest to the ophthalmologist. The neurologist, moreover, wishes to know that quantitative perimetry is a definite, well established procedure of inestimable value when utilized. The paper illustrates this so well that the conclusion of the review as stated is relevant.

SPAETH, Philadelphia.

VARIATIONS IN RETINAL ARTERIAL TENSION FOLLOWING NASAL OPERATIONS. M. GUILLERMIN and G. CHAMS, Rev. d'oto-neuro-opht. **9**:1 (Jan.) 1931.

The idea of Rollet, Sargnon, Colrat and others that, in the nasal treatment for retrobulbar neuritis, the ocular trouble results from vascular spasm led the authors to undertake observations of the retinal arterial tension in patients who had undergone nasal operations of various sorts. The method consisted in observing the diastolic pressure of a retinal artery with the ophthalmodynamometer of Baillert just before the operation, immediately afterward, and twenty-four, forty-eight, seventy-two and eighty-four hours afterward. The anesthetic used had no influence on the pressure.

Forty-two cases were studied. The operations were curettage, cauterizations, turbinectomies and septal operations. In two cases the tension was unchanged. The final result was almost always (92.5 per cent of the cases) a lasting hypotension. In 44.5 per cent, this was preceded by a transient hypertension. The anatomic location of the operation or its nature had no relation to the degree of change of the retinal arterial tension. These results indicate the mechanism of the action of nasal operations in retrobulbar neuritis, namely, utilization of a sympathetic reflex. It is suggested that nasal operations are indicated in ocular

conditions that seem to be allied to a local arterial hypertension, e. g., certain hemorrhages of the vitreous in adolescents in which no general factor can be incriminated, and spasm of the central retinal artery. It is also suggested that the preceding phase of hypertension be counteracted by appropriate medication when necessary.

DENNIS, Colorado Springs, Colo.

THE VALUE OF BRAIN LIPOIDS AS AN INDEX OF BRAIN DEVELOPMENT. FREDERICK TILNEY and JOSHUA ROSETT, Bull. Neurol. Inst., New York **1**:28, 1931.

The authors review the methods used to determine an index of development of the brain as well as previous special studies of lipoids. Sixty-eight human brains were used in the investigation and the method of procedure is outlined in detail. The authors conclude that in man a progressive increase in the lipoids of the brain furnishes a reasonably dependable index for the general status of cerebral development from birth to old age. The total increase is estimated at about 8 per cent. The period of most rapid increase in the lipoids is found during the second year of life, although the lipoids increase irregularly after the first year and reach their highest value in middle age. As the lipoids increase, there is found a nearly proportional decrease in the water content of the brain; the total water decrease is estimated at 10 per cent. In the decades between 60 and 80 there is an appreciable decline in the lipoids of the brain and a corresponding increase in the water content. Determinations of the lipoid content of various portions of the brain were also made and the results are tabulated. No appreciable difference was found between the lipoid content of the right and of the left half of the brain. The influence of disease of the brain on the lipoids is also considered, and it is concluded that infections and nutritional and metabolic disorders of an acute nature tend to diminish the amount, whereas a slight increase seems to mark reaction to more chronic degenerative changes, such as malignant neoplasms and cardiovascular disease.

KUBITSCHEK, St. Louis.

THE APPROACH TO COLLEGE MENTAL HYGIENE. K. E. APPEL and L. H. SMITH, Ment. Hyg. **15**:52 (Jan.) 1931.

Although many of the claims made for mental hygiene seem excessive, there is available a modicum of definite knowledge, which Appel and Smith think should be included in the curriculum of every college student. In the absence of such information the individual is often vexed with the dilemmas of his personality and handicapped by the results of his emotional strife. And yet, in the seven cases reviewed by Appel and Smith, six of the patients turned away from psychology because it touched on sensitive spots, and to one the untutored effort to gain knowledge was detrimental rather then helpful.

The suggested program of mental hygiene consists of: carefully selected, introductory reading both in literature and in psychology; a comprehensive series of lectures on psychoanalysis, behaviorism, Gestalt psychology, endocrine physiology and psychoneuroses and the correlation of thorough social histories of the students with their health and scholastic records.

A committee, composed of the dean and the interested members of the faculty, and assisted by a psychiatrist, could cope with this task. Tactful work by this committee should prove of considerable help in alleviating the maladjustment, so common in college life, and might perhaps prove of value in preventing emotional conflicts in the future.

DAVIDSON, Newark, N. J.

INVESTIGATION OF THE ANTICONVULSIVE POWER OF CALCIUM ALONE OR ASSOCIATED WITH PARATHYROID OR IRRADIATED ERGOSTEROL IN EPILEPTIC PERSONS. F. DI RENZO, Rassegna di studi psichiat. **19**:1029 (Nov.-Dec.) 1930.

The first attempts to use calcium in the treatment for epilepsy were due to Sabbatani, and were followed by the work of others who found a diminution of

calcium in the blood of epileptic persons (Parhon, Longo, Barlocco, and others). Alkalosis emphasizes the diminution of calcium in the blood. Pagniez, Wollmer and Bigwood believed that convulsive seizures are due to the diminution of the iron calcium in the blood as a result of alkalosis. In contrast to the favorable results of the action of calcium on epileptic persons are the reports of Klein and Forcione, who have even found a tendency toward an increase of attacks.

Di Renzo has used various calcium compounds intravenously, or intramuscularly. He used a parathyroid preparation and, as vitamin D, an irradiated ergosterol preparation. Vitamin D and parathyroid substance were given in order to favor the metabolism of calcium and its exchange between blood and tissue so as to produce hypercalcemia. Seventeen cases were studied, and treatment was given for an average of two months. As a result of the investigation the author concludes that epileptic seizures are not favorably influenced by the use of calcium preparations even when the calcium is in the best condition to be assimilated. The conception, therefore, that epileptic seizures are due to hypocalcemia must be discarded.

FERRARO, New York.

INJURIES OF THE BRAIN DURING WAR. M. ISSERLIN, Nervenarzt **3**:569 (Oct. 15) 1930.

The most important and extensive sequel of injuries of the brain sustained during the war is traumatic epilepsy. It may begin at any time after the injury. Most cases are associated with a primary infection of the wound. Even ten and more years can elapse after the healing of the wound before the first epileptic seizures occur. Injuries to the parietal lobe cause the greatest percentage of cases of epilepsy. The prognosis is unfavorable. Blank spells, changes of mood, twilight states, hallucinoses, confusion states and, in a minority, the epileptic alteration of personality, together with severe deliria and status epilepticus are described. Jacksonian phenomena as well as auras are manifold. In many cases, an abscess of the brain may develop years after the injury. Vasomotor and trophic disorders resembling marasmus often appear. Aphasia and memory disorders are also found, with difficulty in motor learning. Foreign bodies in the brain do not dispose to epilepsy as much as does an originally severe injury to the brain. In these cases of trauma to the brain, pseudofunctional and genuinely psychogenic symptoms may appear, the latter being particularly numerous. The person with an injury of the brain tends to acquire functional disturbances. Occupational therapy is useful so long as a personality capable of learning, with moderate energy and stability, remains. Vocational training and guidance are also of value.

HART, Greenwich, Conn.

THE OCCURRENCE OF SO-CALLED "AMYLOID BODIES" IN THE GANGLION CELLS OF THE SUBSTANTIA NIGRA IN POSTENCEPHALITIC PARKINSONISM. E. REDLICH, Monatschr. f. Psychiat. u. Neurol. **75**:129 (March) 1930.

In two cases of parkinsonism following epidemic encephalitis, the author observed corpora amylacea in the pigmented ganglion cells of the substantia nigra. They did not occur elsewhere. A similar observation was made in a case of paralysis agitans. The presence of these inclusion bodies is regarded as an indication of marked cellular damage. The author points out that cases of myoclonic epilepsy regularly show amyloid bodies in the substantia nigra as well as in other parts of the nervous system. Since there is one pathologic feature common to myoclonic epilepsy and parkinsonian conditions, one might expect to find a corresponding resemblance clinically. Such a resemblance does actually occur, for patients with the former disorder often show muscular rigidity. Hence, the author expresses the belief that the muscular rigidity observed in myoclonic epilepsy and parkinsonian conditions is probably produced by alterations of the nerve cells of the substantia nigra. He suggests the possibility that the loss of the pigment normally contained in these cells may be of particular importance in the development of the parkinsonian syndrome.

ROTHSCHILD, Foxborough, Mass.

EPILEPSY AND ITS RATIONAL EXTRA-INSTITUTIONAL TREATMENT. DOUGLAS A. THOM, Am. J. Psychiat. **10**:623 (Jan.) 1931.

Reviewing the various theories of the physiology of convulsive disorders, Thom groups the hypotheses as those which accept cerebral irritation as the underlying cause, those which emphasize deflection of nerve impulses by the interruption of fibers of association, those which assume that chemical changes affect tissues of the brain en masse and those which assign release of lower centers as the basic convulsive process. Most work on epilepsy has been considered from the point of view of patients of the institutional type, whereas 97 per cent of epileptic persons are not institutionalized, and are not deteriorated, psychotic or industrially inefficient. In the treatment for epilepsy, Thom makes a plea for individualization; he suggests careful, honest, thorough examination, frank discussion of diagnosis, prognosis and treatment, creation of an optimistic attitude in the patient and education of himself, his employers and his family to the nature and management of the disease. In discussing this paper, Winkelman expressed curiosity as to the results of this sort of therapy compared to the treatment by dehydration that he and Fay had developed. Thom replied that he was suggesting an individual general approach to supplement the specific treatment offered by ketogenic diet, dehydration or sedative drugs.

DAVIDSON, Newark, N. J.

A CONTRIBUTION TO THE STUDY OF THE PHENOMENON OF FALSE ESTIMATION OF WEIGHTS IN THE MENTALLY DEFECTIVE. ANDRÉ REY, Arch. de psychol. **87**:285, 1930.

When two objects of equal weight but of different volume are presented to the average person, the smaller appears to be heavier. A very young child or a mentally defective person does not find this to be so. The absence of this normal illusion is known as the sign of Demoor. The author studied the reaction to this test in forty-two retarded children between 7 and 15 years of age, of thirty-one normal children between 7 and 14 years of age, and of nineteen children between 5 and 6 years of age, to determine whether retarded children who present the normal reaction really do so, or whether in them the illusion is less marked than in the normal, and whether the same difference exists between younger and older children. He found that when a feebleminded child presented the illusion, the degree of the illusion was much less marked than in the normal child. This was true also of the younger children. The author is not able to offer any suggestion as to the mechanism that produces the illusion, but notes only that its presence indicates a certain degree of intellectual development.

PEARSON, Philadelphia.

MICROGLIA AND OLIGODENDROGLIA IN EXPERIMENTAL INTOXICATION BY HISTAMINE, GUANIDINE, HYDROCHLORIC ACID, THALLIUM AND LEAD. C. UGURGIERI, Rassegna di studi psichiat. **19**:957 (Nov.-Dec.) 1930.

The author, recalling the pathology of oligodendroglia as first described by Penfield and Cone, and the histologic changes described in microglia from poisoning by illuminating gas (Ferraro and Morrison) and lead (Vizioli), has investigated the action of both oligodendroglia and microglia in experimental intoxication with histamine, guanidine, lead, etc. His conclusions, which are based on the study of fourteen rabbits and three dogs, show that in experimentally produced acute intoxication the oligodendroglia always react more or less considerably with degenerative changes of the type of acute swelling. This acute swelling is more pronounced in acute intoxication than in subacute intoxication. On the other hand, the microglia seem not to react at all to the various types of intoxications, except in cases of severe lead poisoning in which even the author is doubtful as to the significance of the acute swelling and breaking of the prolongations in consideration of the fact that there might be a defective impregnation due to the presence of lead in the tissue.

FERRARO, New York.

CARBOHYDRATE METABOLISM IN MONGOLIAN IDIOTS AS EVIDENCE OF ENDOCRINE DYSFUNCTION. W. D. O'LEARY, Am. J. Dis. Child. **41**:544 (March) 1931.

On the hypothesis that mongolian idiocy is related to endocrine dysfunction, particularly to thyroid and pituitary disturbance, O'Leary studied the sugar tolerance in eighteen persons with this form of mental deficiency. Fourteen of the group were receiving treatment with pituitary and thyroid gland, and these patients showed a low sugar tolerance. The other four mongolian idiots were not receiving treatment; they showed an abnormally high tolerance. The curve for the patients receiving treatment with mixed glandular extracts was similar to the curve obtained in hyperfunction of the thyroid and hypophysis. This indicates, that—at least for carbohydrate metabolism—the glands are making their presence felt. Three patients were fed with raw liver for a week; the effect of this diet was to lower the sugar tolerance. O'Leary concludes that mongolian idiots have a hypofunctioning endocrine apparatus, with a high sugar tolerance; that glandular therapy and liver will lower this dextrose curve, and that if mongolian iodiocy is of endocrine origin, it is a polyglandular affection.

DAVIDSON. Newark, N. J.

THE SYNERGISTIC ACTION OF ATROPINE AND EPINEPHRINE ON THE INTRINSIC MUSCLES OF THE EYE. HALLIE HARTGRAVES and P. C. KRONFELD, Arch. Ophth. **5**:212 (Feb.) 1931.

This paper is a discussion of the physiologic and pharmacologic action of atropine and epinephrine on the muscles of the iris. The well known synergy of atropine and cocaine is considered and illustrated. By a combination of atropine and cocaine, of epinephrine and atropine and of epinephrine, cocaine and atropine, and by a comparison of refraction under epinephrine with refraction under atropine, the effects of the drugs were seen and charted. The conclusions that the authors present were derived from these charts and from observations. Epinephrine seems to have no influence on the tonicity of the ciliary muscle, and, therefore, no noticeable influence on the static refraction of the eye, although the range of accommodation is considerably reduced. Epinephrine and cocaine are cycloplegics which prevent, or in smaller doses merely reduce, the contractility of the ciliary muscle, but do not change its original natural tone. Atropine causes the maximum possible relaxation of the ciliary muscle. The failure of epinephrine and cocaine to increase the effect of atropine indicates strongly that the effect of the latter on the ciliary muscle cannot be increased by any method.

SPAETH, Philadelphia.

INDICATIONS FOR AND IMPORTANCE OF VACCINE PYROTHERAPY IN THE TREATMENT OF DEMENTIA PARALYTICA. A. D'ORMEA and E. BROGGI, Rassegna di studi psichiat. **20**:153 (Jan.-Feb.) 1931.

The authors have used intravenous injections of a mixed antipyogenic vaccine of the Instituto Siero Terapico Milanese in cases of dementia paralytica, following the procedure reported by Ciarla and Ventra. This method has been used in cases in which malaria had been previously used, in cases before the treatment with malaria was begun and in cases in which treatment with malaria was never used. Of twenty-five patients so treated, eleven had had malaria. In this group the use of vaccine did not modify the mental picture following malaria. Improvement in the physical condition alone was noticed. Four patients were first treated with the vaccine and then with malaria. The treatment with vaccine helped to establish an improvement in the physical resistance of the patients. Ten patients were treated exclusively with vaccine; of these, five showed a complete remission, one improved, and four remained unchanged.

The author advocates the use of vaccine in early cases. Serologic improvement follows the use of vaccine therapy.

FERRARO, New York.

RADICAL OPERATIONS FOR MAJOR TRIGEMINAL NEURALGIA. CHARLES H. FRAZIER, J. A. M. A. **96**:913 (March 21) 1931.

In this paper Frazier deals briefly with the evolution of the surgical treatment for major trigeminal neuralgia, in order that certain misapprehensions concerning both the risk of the procedure and the ultimate results may be corrected. The major operation has been performed in 654 cases of the author's series of 1,317, and the mortality has been reduced to 0.26 per cent. Since 1901, extirpation of the sensory root has replaced excision of the gasserian ganglion. The technic has been further modified by conservation of the motor root, making possible a bilateral operation when indicated. By subtotal section of the sensory root, the method used by the author since 1915, the area of anesthesia may be limited to the distribution of pain, which in 95 per cent of cases is confined to the two lower divisions of the nerve; thus, trophic keratitis is no longer a menace. When all fasciculi supplying the areas involved are severed, the operation gives complete and permanent relief.

JENKINS, Indianapolis.

A STUDY OF SOME SCHIZOID CHILDREN. A. T. CHILDERS, Ment. Hyg. **15**:106 (Jan.) 1931.

A striking similarity of certain manifestations among a group of problem children to the early symptoms of adult psychoses, and particularly to incipient schizophrenia, prompts Childers to term this type of child "schizoid." Of 114 children under observation, 19 belong to this type. A "schizoid" child lives in a world of exaggerated fantasy. Whereas the life of fantasy, however vivid, of most children disappears with change of mood, with the "schizoid" child it assumes the importance of reality and often develops into mental trends. Hallucinations are common among the "schizoid" group, and there is a sinister definiteness about them. These children desire to be of the opposite sex or to retrogress in age, their dreams are crowded with ideas of escape and of bizarre bodily changes. Childers observed that most of the "schizoid" children were reared by foster parents, or had an unusual position in the family. There seems little doubt that in adulthood these children will manifest schizophrenia.

DAVIDSON, Newark, N. J.

BRAIN ABSCESS AS THE OTOLOGIST'S PROBLEM. O. JASON DIXON, J. A. M. A. **96**:481 (Feb. 14) 1931.

Early diagnosis is an important factor in the management of abscess of the brain. More than 50 per cent of abscesses of the brain are otogenous, three fourths of these occurring as a complication of chronic mastoiditis. A large proportion of cases do not show positive neurologic signs, especially in the earlier stages, and must be diagnosed largely on the history and general symptoms, the most constant of which is uncontrollable headache. Lethargy, a slow respiratory rate, subnormal temperature, vertigo, vomiting, photophobia and slow cerebration are usual. Observations of the spinal fluid are variable and may be determined by an associated meningitis. The author expresses the belief that the fatalistic attitude of otologists and neurologists is unjustified in view of the number of cases in which recovery has resulted from surgical treatment. Recovery occurred in six of this series of twenty-five cases. Illustrative cases are reported in detail.

JENKINS, Indianapolis.

A CONTRIBUTION TO THE STUDY OF THE REACTION OF THE NEUROGLIA AND OF THE NERVE CELLS IN TOXIC MENTAL SYNDROMES. C. A. ROBERTI, Rassegna di studi psichiat. **20**:30 (Jan.-Feb.) 1931.

Roberti concludes that in pure amentia the astrocytes do not show active phenomena in the sense of defense, but undergo passively a gradual decay, more or less rapid, parallel to the lesions of the nerve cells. In cases of mental con-

fusion complicating other diseases, the reaction of the neuroglia may be of a hyperplastic or hypertrophic type. In two cases of schizophrenia the author observed also regressive phenomena involving the astrocytes. Roberti believes that in cases of pure mental confusion, as in amentia and the initial stages of dementia praecox, the neuroglia lacks a defensive power and undergoes a gradual decay. Severe degeneration of the neuroglia or reactive phenomena in the sense of progressive changes are present only when the clinical picture of mental confusion develops in subjects already affected by another disease. In this case the reaction of the astrocytes is influenced by the pathologic changes that are proper to the primary disease.

FERRARO, New York.

THE EFFECTS OF ABSINTH ON THE CAT, FOLLOWING BILATERAL ADRENALECTOMY. H. C. COOMBS, S. B. WORTIS and FRANK H. PIKE, Bull. Neurol. Inst., New York **1**:145, 1931.

This work was done in an attempt to determine the effect of bilateral removal of the adrenal glands on the reaction of animals to a convulsive agent such as absinthe. It was suggested by earlier work on cerebral anemia, which had indicated that general convulsive seizures of unknown origin are caused by vascular changes and that the product of adrenal activity is closely related to the sympathetic mechanism of the vascular system. The experiments were made on a series of cats, and it was found that the minimum convulsive dose was lowered from 33 to 50 per cent by adrenalectomy, while the lethal dose was even more greatly reduced. The results were interpreted as further evidence that removal of the adrenal glands increases cerebral anemia, and they agree essentially with the earlier work of Coombs in 1926.

KUBITSCHEK, St. Louis.

MENTAL DANGERS AMONG COLLEGE STUDENTS. E. D. PHILLIPS, J. Abnorm. Psychol. **25**:3 (April-June) 1930.

Every college should, if possible, have a psychologic clinic where students troubled by difficulties in their studies or in their social adjustments might come for advice. If this is not available, a sympathetic teacher, whose manner can give to the student assurance that he will not be laughed at, can go a long way toward winning the confidence of those whose mental sufferings are making them unhappy. Phillips believes that the roots of many serious, chronic psychoses can be recognized by oddities of thought and behavior during college days, and that it is the duty of every institution of learning to look for these and to correct them. The thesis is illustrated by several case histories of persons who showed peculiarities of manner and thinking in adolescence, and who subsequently developed, or were saved from, frank psychoses.

DAVIDSON, Newark, N. J.

LOCALIZING DIAGNOSIS IN BRAIN TUMOR: PHENOMENA THAT MAY BE MISLEADING. CHARLES E. DOWMAN and W. A. SMITH, J. A. M. A. **96**:318 (Jan.) 1931.

In a series of 183 cases of neoplasms of the brain, verified at operation or at necropsy, the authors found 24 in which misleading phenomena were present. In 4 of the 140 cases of supratentorial tumors, there were symptoms that caused some question as to the side involved; 11 presented signs of cerebellar involvement. On the other hand, 5 cases of tumor of the cerebellum simulated supratentorial lesions. Chiasmal symptoms observed in a temporal and in an occipital tumor were attributed to distention of the third ventricle. Five cases of tumor of the frontal lobe showed homolateral palsy of the fifth nerve with contralateral hemianopia; signs suggesting a lesion of the eighth nerve were present in 6 cases of cerebellar tumor. Accessory methods of diagnosis, especially ventricular estimations and studies of air in the brain, are most valuable in such confusing cases.

JENKINS, Indianapolis.

THE CLINICAL ASPECT OF SEROLOGIC DISCORD IN SYPHILIS. MORRIS A. LYONS, Arch. Dermat. & Syph. **23**:317 (Feb.) 1931.

Of twenty-four patients who were known to have syphilis of the central nervous system, the Wassermann reaction was positive in thirteen and the Kahn reaction in seventeen. These readings were not all four plus, some of the Kahn reactions being as low as one plus. The Vernes flocculation test gave a resultant reading of five or more in fifteen of these cases. All of the specimens that led to a positive Wassermann reaction gave a positive Kahn reaction; and the Kahn reaction was positive in four cases in which the Wassermann reaction was negative. The Vernes test closely paralleled the Wassermann readings. These patients were all under treatment, and the discord in the observations is probably associated with the variation in intensity of the treatment. Lyons concludes that a Wassermann test alone is not a sufficient guide in the diagnosis of and treatment for syphilis.

DAVIDSON, Newark, N. J.

TWO CASES OF TUMOR OF THE POSTERIOR CRANIAL FOSSA CAUSING VISUAL HALLUCINATIONS. EDWIN M. DEERY, Bull. Neurol. Inst., New York **1**:97, 1931.

The author describes two cases of verified neoplasm in the posterior fossa, which are of unusual interest because one of the most prominent symptoms (subjective) was the existence of persistent visual hallucinations. In both cases the patients were of sound mentality, and the presence of visual hallucinations was a complicating factor in the interpretation of the symptoms and localization of the trouble, as a lesion of the temporal lobe was suspected. The author does not doubt the existence of the visual hallucinations, and in discussing the mechanism by which they were caused considers the possibility of an impaired vascular supply to the optic pathway due to pressure on the posterior cerebral artery. However, he does not consider this explanation alone satisfactory.

KUBITSCHEK, St. Louis.

THE IMPORTANCE OF MENTAL HYGIENE IN OTHER DEPARTMENTS OF MEDICAL PRACTICE. MAURICE CRAIG, Ment. Hyg. **14**:565 (July) 1930.

While Craig deplores the failure of medical textbooks and teachers to devote adequate attention to mental hygiene and psychiatry, he emphasizes the importance of the psychologic aspects of daily medical problems. He speaks of the emotional basis of the acidosis of childhood and of the psychic precipitants of the illnesses of adult life. He calls attention to the importance of mental attitude in the patient before operation and to the value of a psychologic understanding of the patient convalescing from operation. He dwells on toxemia and on the mental disorders that it may cause, and he speaks of sleep and sleeplessness as problems of the general practitioner.

DAVIDSON, Newark, N. J.

HERPES ZOSTER OTICUS. T. W. BUCKINGHAM, Arch. Otolaryng. **13**:59 (Jan.) 1931.

Herpes zoster is an inflammation of the posterior root ganglia. A type with facial paralysis was described by Ramsay Hunt. He considered that the geniculate ganglion was similar to a posterior root ganglion, with the pars intermedia of Wrisberg as a sensory root. (J. K. Mills, however, disagreed with this opinion, and thought that these cases were due to an inflammation of the meninges, including the fifth and seventh nerves.) The area involved is the anterior part of the external canal and the auricle. The eighth nerve is frequently affected. Hunt says that the gasserian, geniculate and upper cervical ganglia form a continuous chain. A case is reported.

HUNTER, Philadelphia.

LATERAL SINUS THROMBOSIS COMPLICATING MASKED MASTOIDITIS. IRWIN J. KLEIN and MAX LEDERER, Am. J. Dis. Child. **40**:1045 (Nov.) 1930.

In considering the diagnosis in obscure septic conditions, especially when an infection of the middle ear has occurred, the possibility of a lateral sinus thrombosis may be overlooked. In the case reported by Klein and Lederer, cough, fever and otitis developed in a boy, aged 7 weeks; the skin was cyanotic, the pupils were of pinpoint size and fixed. The temperature rose to 106 F. He had one convulsion, with clonic movements of the right upper extremity and twitching of both sides of the face. At autopsy, a large hemorrhage was found on the anterior surface of the right hemisphere, and a firm thrombus was discovered in both lateral and superior sagittal sinuses. The clinical picture of this complication is not characteristic; the most important features are the high fever, the meningitis-like symptoms and the altered pressure discovered on spinal tap.

A SOCIAL IMPLICATION OF THE GESTALT PSYCHOLOGY. EDITORIAL, J. Abnorm. Psychol. **25**:1 (April-June) 1930.

Deploring the tendency of many psychologists to analyze society into a totality of individuals, the editors of the *Journal of Abnormal and Social Psychology* warn against the danger of falling into the elementary fallacy against which the Gestaltists have been thundering. They view with satisfaction the movement against this "whole is the sum of its parts" psychology, and agree with Koehler that an individual, the stimulating situation and the reaction constitute a single physiologic and dynamic whole. Social research guided by these principles has yielded several fruitful results, and the editors look to it as a promising method of approaching the problems of social dynamics.

THE USE OF SOLUTION OF PITUITARY IN HERPES ZOSTER. D. M. SIDLICK, Arch. Dermat. & Syph. **22**:91 (July) 1930.

By the injection of 1 cc. of obstetrical solution of pituitary on two successive days, Sidlick was able to obtain prompt relief of pain in fifty-four patients suffering from herpes zoster. Since this condition often lasts a month or two, even when treated by roentgen rays, Sidlick expresses the belief that the immediate results of pituitary therapy justify its use. In a few stubborn cases a third injection was necessary. Treatment with solution of pituitary is contraindicated in pregnancy, but otherwise may be used with safety in all patients, even those with hypertension and arteriosclerosis. The herpetic rash disappears within a few days after the first injection.

MEDICOLEGAL COMPLICATIONS OF MALARIA THERAPY. MILOVAU MILOVANOVITCH, Ann. de méd. lég. **9**:658 (Nov.) 1930.

Alarmed by the number of patients with dementia paralytica receiving malaria treatment who have committed suicide, Milovanovitch made a statistical study of this situation in Jugoslavia. He demonstrated that most of these suicides occurred during a partial remission, when the mind of the patient was less clouded and more energetic than it had been previously. He concludes that it is the duty of the physician administering malaria to warn attendants and relatives of this possibility and to insist that vigilance never be relaxed, even when the patient seems much better.

MULTIPLE NEUROFIBROMATOSIS. KIYOSHI HOSOI, Arch. Surg. **22**:258 (Feb.) 1931.

After citing a case of von Recklinghausen's disease that exhibited malignant change after operative intervention, Hosoi reviews the literature on the subject, citing almost 100 references. Of the cases of neurofibromatosis so collected, 13 per cent showed malignant transformation; on the other hand, in some patients

repeated surgical removal of painful fibromas did not cause malignancy to develop. The tumors that did become sarcomatous seldom metastasized. In some instances complete extirpation of a sarcomatous tumor was followed by a malignant change in another fibroma. Von Recklinghausen's disease is generally looked on as a congenital anomaly of the nervous system in a dysontogenetic and hereditary sense.

PARALYSIS OF THE BRACHIAL PLEXUS DUE TO A COLD ABSCESS. CHARLES URECHIA, Arch. internat. de neurol. **3**:371 (Nov.) 1930.

Urechia presents a case of atrophy of the triceps due to a cold abscess at the costovertebral region enveloping the brachial plexus. A diagnosis was made by means of a history suggestive of phthisis and roentgenologic evidence of tuberculous joints at the costovertebral articulations. The abscess, which was palpable just above the clavicle, was tapped.

DAVIDSON, Newark, N. J.

ENORMOUS MUCOCELE OF THE FRONTAL SINUS WITH EXOPHTHALMOS AND HYPEROSTOSIS OF THE ORBITAL BONE. V. VIALEIX, BEYNES and THOUVENET, Ann. d'ocul. **167**:177 (Feb.) 1930.

The mucocele of the frontal sinus started when the child was aged 8. The condition developed so slowly that there were no muscular anomalies and no injury to the optic nerve.

BERENS, New York.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Feb. 10, 1931

MICHAEL OSNATO, M.D., *in the Chair*

The following clinical presentations were from the neuro-endocrine service of the Neurological Institute and Vanderbilt Clinic.

THE LAURENCE-BIEDL SYNDROME. DR. JOHN MCD. MCKINNEY.

A patient came to the Vanderbilt Clinic in October, 1929, because of a nodding spasm of the head, which had been present for five or six months. Examination revealed: Extra digits on the toes; she still had six toes on the left foot, and the mother stated that she had had six toes on the right foot, one of which was removed when she was 4 years of age; the scar was still present. An extra finger on the left hand, which was tied off when she was an infant. She was overweight, 29 pounds (13.2 Kg.), and rather short for her age, being 2 inches (5.08 cm.) shorter than the average. She had difficulty in seeing and a rather high degree of myopia; examination of the retina showed some areas of retinitis pigmentosa. She was backward mentally, with an intelligence quotient of 36. There was a history of a slight increase in thirst, the patient drinking from eight to ten glasses of water in a day, and a relative increase in urination. Neurologic examination showed, in addition to the nodding spasm of the head, twitching movements that were choreiform and more or less generalized, involving both feet and hands, and a spontaneous nystagmus in all meridians, which was present at the time of the meeting.

Roentgenograms of the skull showed that the sella was normal in size, or possibly rather small. Roentgenograms of the extremities showed the extra toe on the left foot, but there was nothing unusual on the right foot or on the hands, although occasionally when such toes are amputated a small spicule of bone is shown on the roentgenograms.

Several cases of this kind have been reported in the literature. The first that I know of were four cases reported before the British Ophthalmological Society in 1866, by two Englishmen, Laurence and Moon, primarily because of the retinitis pigmentosa. However, the patients also showed this short, squat build and they were all members of the same family. Four children of eight were affected. My patient showed all of these phenomena, but no other member of the family was affected. However, there was a brother, the second pregnancy, who died of pneumonia at 13 months, who is said to have had six toes on one foot.

Following the report of Laurence and Moon, in 1866, several other cases of the kind were reported, and in 1921 and 1922, Biedl assembled five or six cases in Germany. In 1925, Solis Cohen and Weiss, in Philadelphia, reported two cases; these authors were the first to use the title employed here.

All the cases show polydactylism, retinitis pigmentosa, mental retardation and the short, squat, fat build. My case differs from the others by the presence of chorea, which has not been reported before, although several of the cases reported showed nystagmus. Another point of interest is that several children in the same family may be affected in the same generation, but no ancestor is similarly affected. Hence this is a familial disease, but not strictly a hereditary one. As regards consanguinity, in two of about eighteen families so far reported, the parents were cousins, but there was nothing of the kind in the family of my patient.

No satisfactory explanation of the cause of this condition has been offered. It is presented here as an endocrine disturbance, mainly because of the therapeutic effects that have been reported from endocrine therapy by some, and not because I think that the endocrine disturbance is the cause. This patient has received extracts of pituitary and thyroid by mouth since October, 1929, and there has been no outstanding improvement so far as can be seen. In the cases reported, the retinitis pigmentosa was the feature that was particularly helped. In my patient this was complicated by a marked near-sightedness which made it difficult to estimate improvement in vision. The weight, 100 pounds (45 Kg.) when the patient was first seen, was 116 pounds (52 Kg.) at the time of presentation. She had grown 2¼ inches (5.14 cm.) in height. The intelligence quotient, which has occasionally been improved in the cases reported, showed a change from 36 to 42 in fifteen months, and the mental age has increased fourteen months in the period of fifteen months, which apparently is a greater rate of improvement than one would otherwise expect.

HYPERGLYCEMIA IN HYPOPITUITARISM, WITH GLANDULAR TREATMENT. DR. JOSEPHINE H. KENYON.

A boy, aged 22, was presented as an interesting example of glandular adjustment. He had been observed since he was 15, first as a patient of the Neurological Institute Clinic and later at the Vanderbilt Clinic. At 15 years of age, in 1924, he presented a typical picture of hypopituitarism; he was a short, fat boy with girdle weight, pads of fat over the region of the breast, a large abdomen and small implanted genitals. He was not doing well in school and complained of frequent frontal headaches. The height was 63 inches (160 cm.) and his weight 153 pounds (69.4 Kg.). (The average weight for his height is 111 pounds [50.3 Kg.].) The blood sugar measured 0.187. Urinalysis, the blood count and other laboratory tests gave negative results. The roentgenogram showed a sella with a heavy dorsum that gave the appearance of closing in of the sella although, due to the separation of the anterior clinoids, this was more apparent than real.

The patient was treated for two years with both whole gland and anterior lobe pituitary extract administered orally and hypodermically. The diet advised was one with a relatively low content of carbohydrate. There was a rapid drop in blood sugar from 0.187 to 0.136 in one month and, when taken at the end of four months, to 0.1. It had varied only slightly from that figure through the succeeding seven years. The urine had never shown sugar. The weight dropped to 128 pounds (57.1 Kg.). After the two years of medication with pituitary was completed, he gradually gained in weight, though on the same diet, but as his height increased in proportion, he never appeared fat again. He lost the pads of fat within the first year of treatment, and when 17 had practically no signs of hypopituitarism.

A roentgenogram of the skull taken recently showed a sella of approximately the usual size for the skull.

He was faithful in reporting at intervals of six months. He graduated from Junior High School, spent six months in a trade school and had been working as a printer ever since.

PLURIGLANDULAR COMPENSATORY SYNDROME. DR. WALTER TIMME.

The case that I shall present is one in which there has been a compensatory progress on a basis of an original inadequacy or on a basis of original inadequacies, dependent on a status hypoplasticus, heretofore known as status thymicolymphaticus.

Patients of this type begin life with many handicaps. The hypoplastic condition is one in which important structures are among the hypoplasias, namely, the pituitary, thyroid, suprarenals, gonads, cardiovascular system, blood vessels, which have an extremely narrow caliber, and heart, which is both ptotic and small. The skeleton is deficient in that the members of the skeleton are loosely bound to the trunk so that the arms and legs are flail-like. The carbon dioxide tension is low.

The polymorphonuclear count is low. The blood sugar and blood pressure are low. These patients—they are not really diseased—are not able to cope with the difficulties of the world and with their competitors. If they remained in this condition, as the years went by they would possibly succumb to some intercurrent disease. But there is a compensatory mechanism that automatically compensates for the difficulties—the group of the hypoplastic structures, particularly the pituitary and the thyroid. If these structures, the pituitary and thyroid, and perhaps the suprarenals, enlarge sufficiently, they overcome many of the difficulties from which the person suffers. The blood pressure increases, the blood sugar increases, the carbon dioxide tension increases and gradually they arrive at a normal level, although it may take a decade or two.

However, coincident with the increase of these glands for compensatory purposes, other symptoms arise that are dependent on the overactivity of these glands; they form part of the finished product and are unavoidable. Not only do the patients grow originally because of the thymus activity, but also later because of the pituitary enlargement. This increase, particularly of the anterior lobe, also causes a rapid increase in the growth of the extremities generally. As the picture changes, and as they grow and definite signs of amelioration appear, they arrive at better and better levels for competition. They may reach an absolutely normal level without knowing what is going on within them unless the compensation fails.

Such patients come to the physician complaining of great fatigue, laxness of the joints resulting in intense backache, flatfoot or intense headache due to the pituitary enlargement. Then the past history and the results of an examination fit them into this particular group of persons who have tried to compensate and have been only partially successful.

The case I shall present is a classic representative of the group. This lad, 18 years of age, came to the hospital last October because of difficulty in locomotion, flatfoot and discomfort of rapidly growing extremities; he also had headaches and more or less fatigability. The family history was not entirely without significance. One ancestor was 6 feet 1 inch (185.4 cm.) in height; another was very heavy; but there was no definite evidence of this particular syndrome. The patient was 6 feet 7 inches (198.5 cm.) tall.

On roentgen examination the sella was much enlarged, though hardly eroded. The pituitary was enlarged because of its compensatory properties, and not because of a neoplasm. The roentgenogram of the chest showed a large shadow in the upper part of the mediastinum, which was possibly partly thymic and possibly a substernal thyroid. He had a greatly enlarged thyroid. The basal metabolic rate was plus 12. The blood pressure was rather low, being about 100 systolic on the afternoon of presentation when he was somewhat excited. The carbon dioxide tension was 48. He had all the earmarks of an original status hypoplasticus with some compensation. The right eye was distorted and injured by an infection with scarlet fever. The left ocular fundus showed the vessels extremely small and narrow; the arteries were like threads. This was so with the vascular system generally. The heart was of the ptotic variety.

This young man was growing, no. only because of the thymus, but also because of the development of a pituitary compensation in addition. He had grown 4 or 5 inches since he was first seen. The epiphyses were still open. The patient was not yet fully compensated but was on the road to it.

Treatment in these cases depends generally on what there is to be done in the way of a compensatory rearrangement. The genitals, while normally implanted, were extremely small. He had very little bodily hair. Following my theory, these rapidly growing patients should be fed with gonads or given injections of various fresh gonadal material, either male or female, or both. It is surprising to see how rapidly the growth begins to cease on their administration. I also irradiate the thymus. Since the previous October, the patient had not grown under this treatment, though he had grown 5 or 6 inches in the preceding year. He had been given some thyroid extract and also iodine. He resembled the giant Turner whom Cushing illustrated in his book, published in 1910 or 1911. At that

time the giant was termed an acromegalic, though he did not have the ordinary type of acromegaly. Post mortem, Turner was found to be thymic, with small blood vessels and a ptotic heart, resembling in many respects the case of my patient.

It is evident that my patient had a marked thyroid enlargement. The teeth were somewhat widely spaced, small and broad. He had large hands that were remarkably hyperextensible. The hyperextensibility of the foot was the condition for which he came to the hospital on account of fatigue in walking. He had the supratrochanteric pads found in hypogonadal states.

DISCUSSION

DR. EMANUEL D. FRIEDMAN: Could not this case be included in the group known in the literature as thymic gigantism?

DR. WALTER TIMME: Partially thymic, yes, but not a purely thymic gigantism. He has also an involvement of the pituitary thyroid and genitals. I understand that thymic gigantism is one in which everything else is within normal limits. This case is much more complicated than simple thymic gigantism.

DR. IRVING PARDEE: I have been watching the patients who have been presented for some time, especially the second one. This case is one of those types of hypopituitary disturbance that show improvement with glandular medication. The patient certainly cannot be called diabetic. The pituitary disturbance was too obvious and too definite, and it was associated with a disturbance in the sugar metabolism, which improved and became normal with glandular medication.

The case of the first patient, whom Dr. McKinney presented, is of interest chiefly as a syndrome. As he has stated, it is a rare condition, only a few similar cases being on record. From the standpoint of endocrinology, I think that there is very little of interest in the case, except that it showed some signs of hypopituitary status. I do not think that one can explain the polydactylism, the retinitis pigmentosa and the remainder of the picture which the patient showed on the basis of an endocrine disturbance.

I should not make any additions to the last case, presented by Dr. Timme. About ten years ago, Dr. Timme first described this syndrome. It is well recognized in the present literature as a pluriglandular compensatory syndrome.

When these patients fail in compensation, a varying glandular picture appears; it may be pituitary, suprarenal, or gonadal in type. Pituitary disturbance on a basis of a thymic inadequacy or status hypoplasticus may show all the signs and symptoms of a pituitary neoplasm. We have treated some of these patients successfully with pituitary medication. Also, acromegaly, Fröhlich's syndrome and less striking pituitary syndromes may appear. In some of the cases, thyroid disturbances present themselves as secondary to thymic disturbances; that is, one may see the adolescent goiter, or a picture of hypothyroidism or hyperthyroidism. Again, in a suprarenal disorder, one may see evidence of marked suprarenal insufficiency, with a low blood pressure, slow pulse, pigmentation and extreme fatigability. When the gonads cause the disorder presented, there is a disturbance which, in the female, shows itself as a disorder of menstruation, difficult and painful menstruation, deficiency in the menstrual flow, etc.; in the male, one may see impotence, undeveloped genitals, undescended testes, etc.

Therefore, although these patients may show a pituitary, thyroidal, gonadal or suprarenal disorder, the real basic disturbance is the status hypoplasticus which Dr. Timme has emphasized.

DISORDERS INDUCED BY INJURY TO THE PITUITARY AND THE HYPOTHALAMUS.

DR. PHILIP E. SMITH.

The pituitary and the hypothalamus are exceedingly complex, both structurally and functionally. Their close topographic association, as well as their hidden location, makes it difficult to injure experimentally one of them only. It is, therefore, not surprising that attention has been focused on one or the other of these structures at different periods and that a major rôle in the genesis of disorders

arising from pathologic changes or experimentally inflicted injuries has been attributed only to one or the other of them. The present tendency seems to be to consider these two structures as an interacting mechanism—the pituitary-neural mechanism. The close association of the pituitary to the hypothalamus, its nervous connection, and its origin and development lend support to the idea that this organ may be more influenced by the negative region of the brain than are the other endocrine glands, and it strengthens the concept of a pituitary-neural complex, the components of which act not independently but dependently. The disorders arising from injuries to this region would therefore not be attributable to one or the other of these structures, but to both. While I do not deny that there may be much truth in this concept, nevertheless, it seems not to be a particularly helpful hypothesis on which to work; it seems wiser to attempt to analyze the function of the hypophysis and hypothalamus independently, even though incurring the danger of being called a "pituitarist" or a "hypothalamist."

I attempted to analyze experimentally the functions of these two structures, using clinical material only through the published reports. Rats were used, although work on monkeys is now being done. Particular attention was paid to general body growth, the reproductive system, the response of certain of the endocrine glands and adiposity. Both the anterior and the posterior pituitary were completely and partially ablated, care being taken to avoid injury to the adjacent region of the brain and, conversely, hypothalamic injuries were inflicted, the pituitary being injured in some of these cases to varying degrees. Pituitary therapy (implants of the fresh glands) was used in both types of experiments.

Twenty-six partial anterior pituitary ablations without injury of the brain were done. The amount of anterior lobe found present at autopsy varied in this series from 0.0009 Gm., or less than one ninth, to over one half of the normal amount. One half, and in cases even less, of the normal amount of anterior lobe, was sufficient to maintain an animal in a normal condition. The animals undergoing severe partial ablations differed markedly from those on which complete ablation was done in their rate of general body growth and in the weight and structure of their thyroids, adrenals and reproductive systems. In none of the cases of partial ablations did obesity or a permanent polyuria develop. This was also true in complete ablation of the anterior and posterior pituitary, except in certain cases in which a slight obesity developed after a period of several months. The obesity, however, appeared to be no greater than that which normally appears with age.

No appreciable effects from ablation of the posterior lobe were noted, even parturition and lactation being normal. In an occasional case there was a slight obesity. Following both anterior and posterior pituitary ablation, whether complete or partial, there was a slight transitory polyuria.

The series of hypothalamic injuries were characterized by obesity and a low grade of polyuria. The obesity varied greatly in degree. It was not correlated with the extent of injury of the anterior or posterior lobe. However, there was a correlation between the extent of the injury of the anterior lobe and the effects on growth of the endocrine and reproductive organs, as in the series of partial hypophysectomies.

Structural studies of the hypothalamus of the rat are so difficult that the localization of the injuries inducing obesity and polyuria has not been determined. Some evidence, which is at present inconclusive, suggests that higher nerve centers may be involved in the induction of obesity. It seems certain that the factor responsible for the early and profound obesity is extrahypophyseal.

The evidence gained from these studies shows rather conclusively that certain effects can be ascribed to an anterior hypophyseal deficiency, others to neural injuries. Although it cannot be denied that the pituitary secretion influences the nerve centers or that the nerve centers influence the activity of the hypophysis—an example being afforded by polyuria—nevertheless, it seems that the functions of the visceral neural centers and of the pituitary can be separately analyzed, and that the influence of one on the other may not be greater than in the cases of the nerve centers and the other endocrine glands.

DISCUSSION

DR. WALTER TIMME: The work of Professor Smith fits in to a larger extent with those who work with cases in human beings. I am particularly interested in the basic reason for the adiposity and the polyuria, the disturbances that used to be considered as hypophyseal; I agree with Professor Smith entirely when he expresses the belief that one ought to determine which of the two is responsible, the hypophysis or the hypothalamus, rather than afford them a joint responsibility. I think that a large part of the difficulty is that it has never been conclusively proved how the secretion of the anterior or the posterior lobe reaches the general circulation. In 1910, Harvey Cushing stated that the secretion of the posterior lobe reached the infundibulum directly with small colloid masses that contain the active secretion, forced through from the margin of the infundibular process, and thus reached the ventricle. These colloid beads were found by Cushing and Goetsch to contain hypophyseal extract.

Since that time, Edinger did some work on the hypophysis which, to my mind, is actually critical. He injected pigment into the posterior lobe of the pituitary and the pigment did not pass into the blood stream or into the third ventricle via the infundibular process. He showed that the secretion from the posterior lobe passed through minute channels between the cells and finally between the glia cells to rather larger vesicles, always between and in the clefts between the glia cells, until the secretion reached the hypothalamus. Harvey Cushing stated that the secretion passed via globules to the edge of the infundibular process and that these forced themselves through the limiting membrane into the third ventricle. That is not so. It is also not true that the secretion goes into the blood stream. It probably passes directly, probably through the lymph channels, to the subthalamic region.

If one injects, disturbs or destroys the hypothalamic region, as Camus and Roussy and Percival Bailey did, there will occur all the symptoms of hypophyseal disturbance, because the hypophyseal secretion to the brain is eliminated. I believe that these operations, like operations on the hypophysis, cut off the secretion from the circulation. If that is so, the hypothalamic operative procedures of destruction did exactly what the destruction of the posterior lobe did; they merely changed the site of the cutting off of the secretory passage.

From Northwestern University, some years ago, came an interesting report in which an autopsy was performed on a patient with obesity and marked diabetes insipidus; only a discrete syphilitic gumma that involved the posterior lobe of the hypophysis was found. No structure of the brain was involved. Serial sections of the entire subthalamic and hypothalamic region were made. The glia cells, ganglia and tracts, were all within normal variation. Only the cells within the pituitary cavity were affected, involving only the posterior lobe. That case is classic and is as good as a mathematical theorem; that is, it needs only one to prove a whole series. Taking this case together with Edinger's demonstration of the way in which the secretion reaches the circulation, one can readily see that those who have supposed the apparent effects of the pituitary to reside in the subthalamic region are wrong. They merely deflected the system at that point.

In regard to the anterior lobe of the hypophysis, it is possible that when one destroys with chromic acid or other irritant a certain amount of tissue, it is not the amount that remains that determines the outcome, it is that amount of tissue free from the resultant scar. How do we know how much secretion can enter the circulation? That must be proved. Until we know this, the amount that reaches the circulation is doubtful.

The situation practically never occurs in which the entire pituitary mass is in the pituitary cavity. A certain amount of it, sometimes as much as from 10 to 15 per cent, lies in the pharyngeal roof and between it and the anterior lobe of the hypophysis. Destroying the tissue in the sella will not do away with the small amount that is still active, and I wonder how that can be weighed against the destruction of the entire anterior lobe.

The relationship of the anterior lobe of the hypophysis and the thyroid, the suprarenal glands and the gonads, is an extremely interesting one, and allows one to apply on that basis and relationship a therapy for many of the disorders of these glands.

There is one statement of Professor Smith to which I take exception from my personal experience. He had no results from feeding anterior lobe of hypophysis to rats. If one feeds human beings, giving the substances hours away from mealtime, one invariably gets an effect, in enhancing growth particularly. When it is fed for months at a time, growth proceeds rapidly, and when this feeding ceases, growth rapidly comes to a level plateau. I am sure that our observations cannot all be amiss, because they are too numerous and controllable.

DR. LEO M. DAVIDOFF: Dr. Smith has modestly presented a number of charts and a number of pictures. I think that he has clarified for all time the relation of the anterior lobe of the pituitary and the hypothalamic region. Dr. Smith has purposely limited his presentation to this relationship. He has not discussed the details of his experiments, which have clarified a great many other points in endocrinology, particularly the relationship of the pituitary gland to the other endocrine glands: the thyroid, the suprarenals and the gonads.

I believe that the work on endocrinology has seen a new epoch since the days when Dr. Evans first published his papers on the production of gigantism in rats by parenteral injection of extracts of the anterior lobe. With that, one was first able to see, experimentally to be sure, but closely in accordance with the clinical picture, gigantism from its incipiency, and one was first able to understand the mechanism of this picture.

From that beginning we have seen the work elaborated in the Harvard laboratories, particularly with regard to the production of gigantism, but later of actual acromegaly in dogs. This work has shown to a striking degree the effect of the oversecretion of the pituitary on the other endocrine glands. Invariably, the acromegalic dogs have enlarged thyroids and enlarged cortical substance of the adrenals. A great many of the acromegalic dogs have a persistent thymus. The effect on the gonads has been variable.

This picture so closely resembles the cases of acromegaly I have had the opportunity of studying at autopsy with Dr. Cushing, that there can be no question of the fact that oversecretion of the anterior lobe of the pituitary produces an increase in the secretion of the thyroid and the suprarenals, not to speak of the thymus. The underfunction of the anterior lobe of the pituitary has the opposite effect on these endocrine organs.

It seems, therefore, that a boy, such as that tall patient, presents a picture of oversecretion of the anterior lobe of the pituitary with secondary effects on these other endocrine glands.

DR. PHILIP E. SMITH: In regard to the pharyngeal hypophysis, this has been described uniformly in man, but no such thing exists in the rat or the dog. A parahypophysis that exists in the dog is in the sella and not in the pharynx. We have investigated this again and again in rats and do not find a pharyngeal hypophysis.

I did not quite understand the point about the partial loss of the anterior pituitary effected in one procedure by destruction with chromic acid and in the other by aspiration through an opening in the sphenoid. In the one case there was obesity and in the other case there was not. I believe that most of us will agree that when one sees healthy and normal-appearing cells, the tissue is functioning, and that is the test which I have applied. All remnants of pituitary have been sectioned and examined, and if the tissue is not sclerotic and the secreting cells show granules, I have concluded that the tissue was functioning.

In regard to the experiments of Edinger, I think that they have always been a puzzle. We must have in mind that they were injections into the general tissue of the hypophysis. It is plain why he should have such results in the posterior lobe. There are nerve tracts there from the brain, and the injected substance followed the path of least resistance. Experimentally, one can take out the

posterior lobe entirely. It has been done in dogs and in rats repeatedly, and there has been no noticeable general effect from the ablation. There are many things that cannot be explained, but certainly after the posterior lobe has been totally removed experimentally, the animals can undergo parturition and raise litters and cannot be distinguished from a normal animal.

I do not want to elaborate further on the feeding of hypophysis. There seems to be a sharp division on this point. An amount of anterior pituitary that is too small to have effect in the normal rat will, when given to the hypophysectomized rat, either intraperitoneally or intramuscularly, have a profound effect. The balance in the endocrine glands seems to have been broken down by the hypophysectomy, and this is a very sensitive test form. Consequently, when we feed as much dried pituitary or fresh pituitary to a rat weighing 250 Gm. as is given to a man weighing 150 pounds (68 Kg.), and no effect is obtained from it, I feel that it was a crucial test. The same tests have been made repeatedly by many investigators in normal rats, and the consensus is that the experimental feeding of anterior lobe is without effect.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 19, 1931

SIDNEY D. WILGUS, M.D., *President, in the Chair*

FEVER TREATMENT FOR DEMENTIA PARALYTICA BY MEANS OF DIATHERMY AND THE ELECTRIC BLANKET. DR. SIDNEY D. WILGUS and DR. LEAH LURIE.

Diathermy.—In a series of ninety-seven patients treated with diathermy, we found 55 per cent much improved, 17 per cent slightly improved and 23 per cent unimproved, as opposed to the rate of spontaneous remission of 3.5 per cent recorded by Raynor. Six patients died as a result of the progress of the disease. Of the improved group, 18 per cent are already at home, and more will follow.

In common with other investigators, we find that the exalted type of patient responds best to treatment, and preferably the more recent cases. Patients from other groups often show improvement, and we believe that patients with manic and other types of the disease should receive adequate treatment. The brains in our fatal cases have not been examined. No patient died directly or indirectly as the result of diathermy.

The beneficial results from treatment with diathermy compare well with those obtained from malaria therapy and all other means, as apparently the fever and not its causative agent is responsible for the results obtained. Diathermy presents a method by which fever can be produced, without infectious or other deleterious toxic substances being used, and with the maximum possibility of control and safety to the patients. The fever episodes should be accompanied and systematically followed by active treatment with tryparsamide or other antisyphilitic remedy, and should be continued for years under careful check. Male patients respond better than do female patients to this treatment.

Electric Blanket.—The Illinois State Psychopathic Institute, which has tried nearly all methods of fever therapy, now asserts that the electric blanket, our original contribution, is the simplest and safest form of all fever-producing agents. The patient is wrapped in ordinary blankets for the purpose of preventing short currents and for the easier production of fever; he is then placed in a large electric blanket with a two-stage (5,000 ma. + 2,400 ma.) control of the current. If he becomes uncomfortable or the fever threatens to rise too high, the current can be modified to meet conditions by means of the two-stage switch. As a rule we leave the current on for one hour and then turn it off for

ten minutes at regular intervals throughout the treatment. When the temperature reaches 102.8 F., the current is turned off, but the temperature continues to rise to between 104 and 105 F.; then after one hour we begin to unwrap the patient. With this method we are able to bring about the exact fever curve produced with diathermy and other agents, with absolute safety and accuracy.

Of thirty-one patients under treatment, 10 per cent promptly showed marked improvement, as opposed to 11 per cent in the series treated with diathermy; 39 per cent showed good improvement, as against 44 per cent in the other series; 22 per cent showed appreciable improvement, against 17 per cent, and 23 per cent were not improved, against 22 per cent. As in the group treated with diathermy, 5 per cent of the patients died; death had no relation to the treatment, except in one patient who passed into convulsions at the height of the first treatment.

The serologic and other results obtained from diathermy therapy hold true with the electric blanket treatment, and tryparsamide therapy should be used as in other fever treatments.

Fever therapy with the electric blanket, while not spectacular, is simple, safe and efficient, and we consider it superior to any previously used method for the production of fever.

DISCUSSION

DR. CLARENCE A. NEYMANN: The machine that I used varies somewhat from the one employed by Dr. Wilgus. It can develop from 6,000 to 8,000 ma., or about double the power that Dr. Wilgus uses. It seemed to us that the extent of time the temperature is kept at a high level is most important. The total number of treatments is also important. We believe that these should not be limited to twelve, for we have seen many remissions occur after twenty-five treatments in patients who did not show much improvement before. If Dr. Wilgus would give a greater number of treatments to the patients who do not respond, and would extend the height and the time of the fever reaction, I believe that he would achieve better results.

The electrodes are a matter of choice. We used smaller electrodes in the beginning of our work, and encountered a large number of burns, particularly whenever we employed currents of 500 kilocycles and 8,000 ma. We now use a split electrode for the front with a rheostat, which allows us to apply up to 8,000 ma. with safety. Thus the temperature can be raised to 105 F. in about three quarters of an hour.

Mr. Osborne and I did the first experimental work with animals. This was begun in 1927, and a report was published in the *Illinois State Medical Journal* in September, 1929. Dr. Ivy and Dr. Mortimer employed a radio oscillator, which does not have electrodes, but sends a radio current through the body. This interesting research was begun after our results had been published.

The results vary with the material. We agree with Dr. Wilgus that early cases of dementia paralytica, especially of grandiose type, give the greatest number of remissions. The slowly dementing types react next best, while the depressed types are slow to respond to treatment. The electric blanket was demonstrated in my presence about eighteen months ago. I have not employed it. Perhaps it offers a simple way of producing artificial fever. The important question is: How long can the temperature be maintained by this means? With our diathermy machine we can maintain a fever for nine hours, ranging between 103.5 and 105.5 F. The length of such a fever and the number of treatments are the true criteria. The results obtained must be credited to heat.

DR. PETER BASSOE: One point about the history of this treatment is that Wagner von Jauregg was not the first to induce fever in the treatment for mental disease. Between 1860 and 1870, Dr. Rosenblum, of Odessa, inoculated the organisms of relapsing fever, malaria and typhoid into patients with dementia paralytica. He did not publish a report of this method at the time, for he thought that it would not be safe for him to live in Odessa if he did, but in 1876 he wrote an account of it and published it in the *Odessa Hospital Bulletin*. A translation of this paper by Oks appeared in 1879 in the *Archiv für Psychiatrie*.

DR. CHARLES F. READ: Since I have been at Elgin I have had ample opportunity to observe diathermy in the treatment for mental disease, and can thoroughly corroborate all that has been said this evening. It is a clean and useful type of therapy. I have been particularly interested in the use of the electric blanket, and hope that you will remember what has been said about it. It seems to be a simple and efficient way of securing a heat reaction in the human body, and is apparently without particular drawbacks. I have recently ordered two blankets for use in other parts of the hospital, and expect to make constant use of them.

I was interested in what Dr. Neymann said regarding the length of time during which the fever is maintained, particularly as this applies to the use of suspensions of sulphur in oil, with which one does not obtain a high temperature but a fever that is maintained at over 101.5 F. for long periods of time, even for from twenty-four to thirty-six hours at times. In our small series we had about the same results that are reported from the use of diathermy. I think the maintenance of the temperature over some length of time is a considerable factor in the results obtained.

DR. SIDNEY D. WILGUS: Has Dr. Neymann any figures to show that the prolonged fever had any effect in increasing the favorable results?

DR. CLARENCE A. NEYMANN: In the beginning we did not know what our results would be. The work was begun in an effort to prove whether the fever or the foreign protein was the active therapeutic agent. At first we gave only a few treatments, and remissions were few. Gradually the number of treatments was increased and the time of each treatment was extended. Our good results increased. Finally, we selected the best types of patients for treatment. Now, with such selected material, our rate of remissions is about 75 per cent. We always inform patients that they must take from thirty to forty treatments. A number of patients have received fifty treatments without injury. Thus, it would seem that the rate of remission increases as more intensive treatment is given. At present we aim to treat a patient until the case either proves absolutely hopeless or shows a remission. After a remission has occurred we usually give three final treatments.

DR. SIDNEY D. WILGUS: The most likely theory behind this treatment is that the fever brings about some change in the spirochetes and, organically, in the endothelial system of the host.

CONTINUOUS RHYTHMIC MOVEMENTS OF THE PALATE, PHARYNX AND LARYNX. DR. NORMAN LESHIN and DR. T. T. STONE (by invitation).

This article will appear in full in a later issue of the ARCHIVES.

SPINAL CORD CHANGES IN LYMPHOGRANULOMATOSIS. ARTHUR WEIL.

This article will appear in full in a later issue of the ARCHIVES.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 27, 1931

JOSEPH MCIVER, M.D., *President, in the Chair*

BROWN-SÉQUARD PARALYSIS FOLLOWING A PARAVERTEBRAL ALCOHOL INJECTION FOR ANGINA PECTORIS. Presented by DR. MATTHEW MOLITCH and DR. GEORGE WILSON.

This paper appeared in *The Journal of the American Medical Association* **97:** 247 (July 25) 1931.

JUVENILE DEMENTIA PARALYTICA OCCURRING IN THE THIRD GENERATION OF A SYPHILITIC FAMILY. Presented by DR. FREDERIC H. LEAVITT.

This patient was of interest because he presented mental and physical signs of dementia paralytica, developing at about the age of 6; because his maternal grandmother died of the tabetic type of dementia paralytica in 1922, and because her daughter (the mother of the patient) also suffered from congenital syphilis during infancy and childhood and during the past few years had been a patient at the Wills Hospital in Philadelphia suffering with syphilitic disease of the optic nerves. The Wassermann reaction of the blood of the father and mother were negative, but the reports on the spinal fluid of the mother and maternal grandmother gave a positive reaction of +4. The Wassermann reaction of the blood of the patient was +4; a report on the spinal fluid showed a positive Wassermann reaction of +4, 40 cells and a colloidal gold curve of 5,554,321,000. We considered that this indicated the development of juvenile dementia paralytica as a result of an infection originating at least with the maternal grandmother.

The patient had seemed like an average child mentally and physically until he was 6 years of age, when he had scarlet fever. Soon after this he became listless and gradually deteriorated mentally. Since 1928, when he was in the fourth grade, he had failed of promotion in school. In 1929, he was demoted to the third grade, and in 1930, it was necessary to place him in the second grade. In 1931, he was found unable to do the work in the first grade at school.

The patient had one healthy brother, aged 5, and the mother had had a miscarriage prior to his birth. The patient was born at term with the aid of forceps. He started to walk and talk at 15 and 12 months of age, respectively. During the past year several attacks occurred in which there was loss of consciousness with general rigidity lasting for several minutes. On examination, he was poorly nourished and developed. The essential physical abnormalities were: decided dysarthria, especially on test phrases; unequal, irregular pupils, reacting very sluggishly to light and well in accommodation, and exaggerated knee jerks, devoid of spasticity. Other results of physical examination were of no moment. Mentally, he was euphoric; he had a constant sense of well being and was unduly happy at all times. It was impossible for him to carry on a conversation, and his memory was poor both for recent and distant events. No delusions or hallucinations were present.

Because of the progressive mental deterioration, the sense of well being, the physical signs in the pupils and knee jerks and the positive serology of the blood and spinal fluid, a diagnosis of juvenile dementia paralytica occurring in the third generation of syphilis was made.

DISCUSSION

DR. C. W. BURR: Dr. Leavitt covered the one interesting point, namely, syphilis in three generations, dementia paralytica in the first and third and neurosyphilis without dementia paralytica in the second. The child's smiling and laughing are not mere reflexes; they are a manifestation of euphoria, an emotional symptom of the dementia paralytica. The conduct agrees with his physical (reflex) signs of happiness; in reflex laughing and crying, conduct does not correspond with the reflex.

DR. J. MCIVER: I have had two patients with congenital syphilis to whom inoculations of malaria were given. Each had several chills, but neither showed improvement. One patient had a case of bilateral involvement of the eighth nerve and the other, a case of juvenile dementia paralytica.

DR. W. FREEMAN: The smiling and laughing is particularly interesting. It is not exactly like the involuntary, spasmodic type of laugh, such as one sees in multiple sclerosis or pseudobulbar palsy. The laughter does not come in paroxysms, but appears to be more or less involuntary.

Concerning malaria in the treatment for dementia paralytica in juveniles, I have had several patients who were inoculated with malaria without resultant paroxysms.

DR. S. GILPIN: I understand that the mother of this child had syphilis of the eye. Was the lesion a primary optic atrophy?

DR. F. H. LEAVITT: The records of the Wills Hospital did not give the exact condition of the eye for which the mother of this patient was treated. Malarial treatment of dementia paralytica in juveniles has not given beneficial results in my hands or in those of others, according to the literature.

TWO CASES OF HEREDITARY CEREBELLAR ATAXIA WITH INTERESTING ENCEPHALOGRAPHIC OBSERVATIONS. Presented by DR. SAMUEL B. HADDEN.

I shall present two patients from the service of Dr. George Wilson in the Episcopal Hospital with encephalographic plates made by Dr. Ralph Bromer. The patients are brothers. Stanley, the older, is 43; he first came to the dispensary in April, 1930, complaining of a staggering gait and difficulty with speech. He dated the onset of the condition from about the age of 35, but his wife stated that before he became aware of his unsteady gait clumsiness in all movements had been noticed for several years. Slurring of speech had become noticeable in the last year, and for about six months he had complained of slight impairment of vision. The previous medical history was not significant. In addition to the brother presented who had the same condition, there was a maternal uncle who "could not walk very well."

Aside from marked oral sepsis, physical examination gave essentially negative results. The pupils were round, equal and regular, and reacted promptly to light and in accommodation. The eyegrounds were normal, and the visual fields were normal to rough tests. The ocular movements were normal. There was no nystagmus. The patellar reflexes were moderately exaggerated. The plantar reflexes were normal. There was slight incoordination in the finger-to-nose test, with distinct adiadokokinesis. There was a rolling cerebellar gait and an abnormal swaying in standing with the eyes closed. A few mistakes were made in calling the position of the fingers, but vibration, touch and pain were normally interpreted. Astereognosis was not observed. Aside from the symptoms cited, all other details of the neurologic examination were normal.

An encephalogram was performed by the closed system replacement method, and 220 cc. of fluid was removed.

The other brother, Paul, was a patient in the dispensary of the Jefferson Hospital, and through the courtesy of Dr. Burns and Dr. Gilpin we were allowed to study him. This brother was 41 years of age, and presented the same symptoms, but to a more advanced degree. He dated the onset of ataxia from the age of 16. At that time he became conscious of clumsiness, which had gradually progressed. He expressed the belief that his speech had been slurring since the onset.

In February, 1920, he was studied in the University Hospital, and at that time he presented essentially the same symptoms as he showed at the time of presentation. However, the spinal fluid gave strongly positive reactions, and he was treated for a period of time; then, in October, 1928, he reported to the Jefferson Hospital, where several positive Wassermann reactions were secured with the spinal fluid.

As in Stanley, examination of the eyes showed no abnormality. The patellar reflexes were exaggerated, and an indefinite response was obtained to plantar irritation on both sides. There was more pronounced ataxia in the finger-to-nose test, and the station and gait were also more markedly disturbed. There was no disturbance of touch, pain position, vibration or stereognosis. An encephalogram was made, and 230 cc. of fluid was removed. The encephalograms of both patients were presented.

The most remarkable observations in the encephalograms were the marked atrophy of the cerebellum and the advanced cortical atrophy, especially in the parietal lobes, though there was little clinical evidence of disturbance in this area. In the case of the brother with syphilis, the cortical pathways were less marked than in the other. In both patients, the atrophy of the cortex extended much further posteriorly over the occipital lobes than is common.

DISCUSSION

DR. W. G. SPILLER: That incoordination may result from a lesion of the parietal lobe may be accepted. In Dr. Hadden's cases it is difficult to distinguish symptomatically the relative importance of the atrophy of the cerebellum and that of the parietal lobe; in each of the two brothers the atrophy of the cerebellum and the parietal lobe was bilateral. It seems probable that the cerebral atrophy implicates more than the parietal lobe.

The diminution in size of one cerebellar hemisphere, with defective development of the opposite cerebral hemisphere, arrested my attention in 1902, when I reported the observation of unilateral internal hydrocephalus of the right cerebral hemisphere, acquired early in life, with markedly defective development of the left cerebellar hemisphere. Since that time, I have published reports of similar cases. The anatomic connection between these two parts of the brain may be explained, especially by the internal and the external bundles of the pes pedunculi. The former has been described as the tractus frontopontinus (Obersteiner) and has been believed to represent a bundle of fibers from the frontal lobe through the anterior limb of the internal capsule to the pons, though this has been disputed by Dejerine. The latter, called by Dejerine the fasciculus of Türck, has been shown by him to arise from the second and possibly third temporal and from occipital convolutions and to degenerate downward from a lesion low in the internal capsule. I have seen his sections presenting degeneration of this bundle from such a lesion. This tract terminates in the pons, but both tracts probably have a connection through the middle cerebellar peduncle with the cerebellum.

DR. S. GILPIN: I think that there is no doubt that the brother whom we had under care at the Jefferson Hospital had syphilis. We were furnished with a copy of the history from the University Hospital in which the spinal fluid was reported positive. I believe that he was treated for some time after this. A number of years afterward, he came under my observation. At this time the Wassermann reaction of the spinal fluid was +3. He improved under treatment, and tonight walks better than he did at the Jefferson Hospital two years ago.

DR. T. FAY: This is a beautiful demonstration of two things: Cerebellar atrophy of this type is usually associated with a marked degree of parietal atrophy. When the parietal atrophy occurs alone, few symptoms are present, and the same may be said regarding the cerebellar atrophy. There is a striking absence of the symptoms that one would ordinarily attribute to lesions in this area, probably because it is a selective type of atrophy, with compensation through other structures. I recall a case of Dr. Freeman's, presented to this society, in which the cerebellar hemispheres were congenitally absent, without striking symptoms of ataxia. I also recall a case that Dr. Freeman referred to me for study in which an encephalogram showed biparietal atrophy with some cerebellar atrophy, giving marked symptoms of ataxia similar to those described by Dr. Hadden in his patients. When there is a combined picture of parietal lobe atrophy with cerebellar atrophy, the clinical symptoms become very striking.

DR. W. FREEMAN: Is there associated disease of the posterior columns in these cases? Some of the symptoms make it seem closely related to Friedreich's disease. There is a suggestion of weakness and also the possibility of atrophy. What Dr. Fay has said about the importance of the parietal lobe is of definite interest in this regard and I have brought some sections of a case of cerebellar agenesis that indicate an overdevelopment of the proprioceptive system. I believe that one can get the most serious results from cerebellar disease, providing the posterior columns or parietal lobes are degenerated.

DR. S. B. HADDEN: Despite the remarkable atrophy of the parietal area, there are no sensory changes. The patients showed mild mental changes, especially changes in judgment. The older of the two, the one whose Wassermann reaction was negative, recently received a sum of money from a former employer. He paid a year's rent in advance, using the whole sum and leaving nothing for food

and clothing, knowing that there was no other source of income. Both patients showed marked exaggeration of patellar reflexes. This is the only sign other than cerebellar ones that they present.

Unilateral Myoclonic Movements Probably of Encephalitic Origin.

Presented by Dr. Alfred Gordon.

The interpretation of clinical symptoms on the basis of pathologic lesions is not always satisfactory. This is particularly evident in the generally adopted attempts to explain abnormal muscular movements by invasion of the basal ganglia and especially of the striatal system. The efforts in that direction date from the time when an intense interest was aroused in the study of epidemic encephalitis, though Brissaud long before intimated the probability of such a localization. Myoclonia, which is characterized by spontaneous, abrupt and rapid muscular contractions, is not infrequently observed in the course of encephalitis. Nevertheless, its localization may not always be in the anatomic area characteristic of encephalitis. The exclusive tendency to incriminate the corpus striatum is not justifiable because it is not always pathologically correct. The subject deserves analysis and discussion. The case to be described is an example of unilateral myoclonia and will serve as a basis for a critical consideration.

Mrs. V. M., aged 60, had contracted what she called "the grip" about seven months prior to presentation. She had a cough and a slight elevation of temperature, which lasted for several weeks. During convalescence she suddenly observed a slight awkwardness in both right extremities. She soon recovered, but a gradually oncoming tremor developed in the same areas.

Examination showed normal gait and station, an increased knee jerk on the right side, absence of ankle clonus and a normal plantar reflex on both sides. The right arm and leg were the seat of involuntary myoclonic contractions, which were rhythmic and regular. It was observed that these muscular movements increased in intensity when passive or active motions were provoked in any part of the body. When the hand was supported, as, for example, by placing it on the patient's knee, the myoclonic movements were directed inward and outward. When the arm was outstretched and not supported, the wrist and hand showed extensor and flexor movements. The same upward and downward movements were observed in the foot; the heel was raised off the floor and lowered repeatedly.

The patient's sensibility was intact for superficial and deep sensations. Astereognosis was not noted in the right hand. Arteriosclerosis was evident. The second aortic sound was accentuated. The eyegrounds showed a blurred disk and contracted arteries on the left, as well as some lenticular haze. The Wassermann reaction of the blood was negative. There was a slight anemia — hemoglobin, 75 per cent; red cells, 3,930,000; white cells, 5,000. The sphincters were intact. The patient was subject to attacks of vertigo. The mentality was good.

This patient presented other interesting phenomena, namely, frequent hiccup and abundant salivation. Both symptoms dated from the time of the onset of the hemimyoclonia. It was interesting to note that when, on the occasions mentioned, the myoclonia was increased, these two symptoms also increased in frequency and intensity.

Finally, the musculature of the two affected limbs had undergone atrophy, in spite of the fact that the power of each individual segment of the limbs was fairly well preserved and that the patient did not require assistance in feeding and dressing herself.

Comment.—The slight hemiparesis, which occurred suddenly in the beginning, is naturally referable to an involvement of the corticospinal or pyramidal tract. Whether this involvement was a destructive lesion or only a disturbance of function one cannot definitely say in view of the absence of histologic verification. However, the patient recovered promptly from the sudden insult; the motor power was greatly restored, and only a slight disturbance remained for a short while and finally disappeared. Instead of it, well regulated, rhythmic, myoclonic movements appeared on the affected side. The question is whether or not the myoclonia

was due to the same functional or lesional disturbance that produced the initial hemiparesis. If one bears in mind experimental cerebral physiology, one must admit that the motor cortex does not take part in the great variety of involuntary muscular movements, such as myoclonia, athetosis or chorea. In decerebration, for example, such phenomena are absent. In the decerebrate rigidity of man they are absent. Magnus stated that he has never observed them in lower animals that he has decerebrated. Moreover, in clinical neurology, it is extremely rare to observe these involuntary movements in the extremities that are affected with total pyramidal paralysis. It seems, therefore, that the efferent pathways or the motor mechanism must necessarily be intact in order that the motor involuntary manifestations can be present. Therefore, in such cases the stimulation of the motor mechanism comes from the afferent pathways, which in all such cases must be disturbed either functionally or organically, and the lesion may be situated at any level along the entire pathway. The afferent fibers for the efferent tract come from the cerebellum, with relays in the subthalamic region and thalamus itself. Herz reported a case of athetosis in which a small circumscribed lesion was found in the thalamus. In one case of aplasia of the cerebellum and in another of absence of the cerebellum on one side, Mingazzini found degenerated or aplastic areas in the homolateral and contralateral transverse fibers of the pons, in the fibers of the mesial and lateral fifth of the pes pedunculi and in the anterior segment of the internal capsule. All of these observations naturally lead to the opinion that the cerebellocerebral tract from one end to the other is a transmission apparatus, a disturbance of which will result in myoclonia, choreic or athetotic movements, provided there is integrity of the efferent or the corticopyramidal system.

As to the striatal system, which since the advent of epidemic encephalitis has been frequently incriminated in many postencephalitic sequelae, it is sufficient to recall among the most recent observations that of Kinnier Wilson (*Deutsche Ztschr. f. Nervenh.* **107**:28 [Dec.] 1928) in which he gave the history of a woman whose right side was affected with choreic movements. Postmortem examination showed a shrunken postcentral convolution; both corpora striata were well preserved macroscopically and microscopically. The left putamen was histologically intact. Wilson's observation, therefore, speaks in favor of the view I have mentioned, that it is not the efferent tract which is involved in unilateral chorea, but that it is the afferent system, and in his particular case a sensory portion of the long pathway, that is, the postcentral convolution. Wilson's case is a strong argument against the frequent assumption concerning the striatal system as being the cause of involuntary movement.

The conclusion, to which the considerations mentioned may lead is that all conditions in which abnormal motor discharge is manifested in involuntary muscular movements, such as chorea, athetosis, myoclonia and others, are due to a disturbance in the centripetal regulation of any portion of the long cerebellocerebral pathway, but the centrifugal or the corticopyramidal system must be preserved intact.

As to the nature of the disorder in the case described here, in view of the acute febrile onset, it was presumably infectious in character and affected the already damaged blood vessels (arteriosclerosis) of the cerebripetal pathway.

It remains now to explain the state of the musculature on the affected side, which was undergoing atrophy imperceptibly. The patient was righthanded and continued to exercise the arm and leg; in spite of this the musculature was flabby. Cases have been reported in which myopathic disturbances parallel with myoclonia of the involved musculature have been present. Histologic examination of those muscles showed the existence of degenerative lesions with loss of striation in some fibers. Sometimes the muscular fibers are hypertrophied and the nuclei are increased in number (Moniz, E.: *Rev. neurol.*, 1930, no 5, p. 747). The pathogenesis of all such cases is obscure. If the myopathic disorder is first to appear and the myoclonia next, the latter may be of peripheral origin. In the case that I have described, the slight myopathic disorder developed simultaneously with the myoclonia, thus indicating a double influence of the affected afferent tract, that is, central and peripheral.

CEREBRAL MUSCULAR ATROPHY AS A SIGNIFICANT SIGN OF TUMOR OF THE PARIETAL LOBE WITH PRESENTATION OF CASES. DR. A. SILVERSTEIN.

During the December meeting of the Philadelphia Neurological Society I presented a report on a series of cases of tumor of the brain in which atrophy of the muscles was present in the paralyzed extremities and was associated with astereognosis and other sensory changes. I was not prepared at that time to report any instance in which atrophy was present without motor symptoms. The following cases are examples of this type and are presented as proof that in our reported cases atrophy of the muscles is a sign of involvement of the parietal lobe. The first case is of great interest in that peripheral atrophy was the only neurologic sign in a confirmed diagnosis of tumor of the parietal lobe.

CASE 1.—*History.*—C. H., a girl, aged 12, was referred by Dr. O. B. Large, to the neurologic service of Dr. Winkelman, at Temple University Hospital, on Jan. 5, 1931, complaining of convulsive seizures. The past medical history was practically without importance. The patient was one of five children whose parents were both deaf mutes. She was normal in every way until about 2 years of age, when she was dropped from the arms of a nurse and apparently was only injured slightly. Soon after the fall, the child had an attack in which the left lower limb became stiff and jerked. This lasted for about fifteen minutes, without loss of consciousness. The seizures became as frequent as ten per day, and occasionally the jacksonian attacks were followed by a generalized convulsion. A letter from Dr. Kramer of Akron, Ohio, who saw the patient at this time, stated that his diagnosis was "epilepsy with mental retardation." Complete studies of the blood and spinal fluid gave negative results. The patient responded well to medication with phenobarbital and was under this treatment for the entire summer of that year; she remained absolutely free from all symptoms for eight years.

In November, 1930, she had a recurrence of the condition. The patient had as many as eleven focal jacksonian seizures of the left lower limb in a week and about one generalized convulsion a month. The seizures began with a tapping of the left foot against the floor, with contractions gradually increasing in severity, which left weakness of the left side of the body. There was no loss of consciousness, no frothing at the mouth and no incontinence during any of the seizures. She would, however, occasionally injure herself in falling during the spells. At no time did she have headache, vomiting or any other symptoms. During the interval between seizures, she seemed to be normal in every way. Incidentally, the patient stated that she noticed that the left hand was smaller than the right because of differences in the fit of her gloves.

Physical Examination.—The heart, lungs and abdomen were practically normal. The skull gave a dull percussion note over the right parietal bone.

Neurologic Examination: The olfactory sense was normal on both sides. There was slight blurring of the disks. The pupils were equal and responded to light and in accommodation. There were some slight nystagmoid jerks when looking laterally. When the patient pulled up the corners of the mouth there was evidence of slight weakness of the left lower part of the face. The tongue protruded in the midline, and the soft palate was raised equally on both sides.

In the upper extremities, the dynamometer readings were: right hand, 40; left hand, 32. The most significant and practically the only observation was definite atrophy of the muscles of the left upper extremity. The left hand and forearm were smaller and appeared to have softer and more delicate skin than the right. There was no weakness in the lower extremities. She was able to stand on either leg without difficulty. The finger-to-nose test and heel-to-knee tests were well performed. The left leg was slightly smaller than the right. The biceps and triceps reflexes were practically equal on the two sides. There was no Hoffman sign. On stroking the sole of the left foot there was a tendency to separate the toes, without movement of the big toe. The abdominal reflexes were active and equal on the two sides. The patient was able to recognize readily the slightest degree of change in the position of the fingers on both sides. Also, passive motion, touch, vibratory sense, two point discrimination and stereognosis

were all intact. Pin prick was felt normally, with a possible slight hypesthesia of the little and ring fingers of the left hand. There was no hypotonia.

A roentgenogram of the skull taken on Jan. 6, 1931, showed flaky and flocculent calcification in the brain, high up in the right parietal region near the vertex. It extended nearly 2 cm. from the midsagittal plane. Just below and anterior to these markings a linear calcification was found. Dr. Chamberlain reported that the flocculent character of the density made it most likely that we were dealing with calcification in a glioma in the upper right parietal area, and ventured a diagnosis of oligodendroglioma.

Examination of the spinal fluid showed an initial pressure of 16 mm. of mercury and 5 cells per cubic millimeter. The Wassermann reactions of blood and spinal fluid were negative. The blood count showed: 74 per cent hemoglobin and 3,800,000 red cells. Study of the electrical reactions of the atrophied muscles revealed a marked quantitative diminution in response to stimulation, but no qualitative disturbance.

Roentgenograms of the hands revealed that the bones of the left hand were shorter and smaller than those of the right. The left hand possessed less soft tissue than its mate.

Operation and Course.—On Jan. 16, 1931, the patient was operated on by Dr. Temple Fay who reported: Close to the midline and just posterior to the rolandic fissure the convolutions had a distinctly greenish appearance. One half centimeter below this cortical discoloration a well encapsulated cyst was encountered containing bright yellow fluid with many sparkling flakes of crystals. A nubbin of tissue projected into the cyst from the upper posterior aspect. The cyst was evacuated. The wall of the cyst was then carefully dissected free from the brain tissue. Posteriorly, the tissue became firm and invaded the brain. This was dissected free. A defect, about the size of a golf ball, remained where the cystic tumor had been removed. Pathologic examination of the tumor by Dr. Winkelman proved this to be a typical oligodendroglioma with calcification and cystic degeneration.

The patient appeared well following the operation, and her only discomfort was pain at the site of the incision. On January 20, a left hemiplegia developed. She had paralysis of the left lower part of the face, with a complete flaccid involvement of the left upper extremity and weakness of the left lower limb, as evidenced by an external rotation of the limb (the latter, a sign that Dr. Winkelman has emphasized in cases of disturbance of the pyramidal tract). The biceps and triceps reflexes were lost; there was no Hoffman sign. The left patellar reflex was increased, with a positive Babinski sign. There was marked sensory loss. Astereognosis was complete; sense of position, passive motion and touch were lost. Vibratory sense and sense of pin prick were diminished on the left side. The atrophy of the left upper extremity was more pronounced. An inspection of the wound revealed edema of the flap, but did not show increased tension. The patient improved rapidly. The motor function was the first to return. Examination by Dr. Winkelman revealed the following signs: There was evidence of a slight weakness of the left lower part of the face. The grasp of the left hand seemed weaker, but dynamometer readings were: right, 34, and left, 30. The biceps reflex was slightly more prompt on the left side, and the patellar reflexes were equal on the two sides. The abdominal reflexes were diminished on the left side, and on stroking the sole of the left foot, there was a tendency to upward extension of the big toe. The left upper extremity showed marked incoordination and awkwardness in movement. The ataxia was present when the eyes were open, but was worse when they were closed. Astereognosis was complete, and other sensory changes were practically the same as at the previous examination. The atrophy was still marked. The patient was discharged on Feb. 2, 1931.

Examinations in the outpatient neurologic clinic showed a progressive improvement in the symptoms. On February 3, there was no evidence of sensory or pyramidal tract disturbances.

Comment.—In analyzing the case, a number of features are striking: first, the existence of a tumor of such size producing so little general and local signs with complete freedom from all symptoms for eight years. This may be explained by the type of lesion. According to Bailey and Cushing, the oligodendrogliomas are very rare, beginning early in life, and are of slow growth; they do not produce pressure but have a tendency to calcification. It is because of the latter characteristic that these tumors are usually rendered visible on roentgen examination. In contrast to the preoperative lack of positive signs, the marked motor, sensory and trophic disturbances following the operation should be considered. The tumor was located in the anterior portion of the superior parietal lobe, and gave as its only sign a trophic disorder of the opposite extremity. It is noteworthy that the hemiplegia that was present in this patient with the absence of biceps reflex and flaccidity is the type that we have commonly seen in advanced cases of tumors of the parietal lobe associated with atrophy. After studying the roentgenograms in this case, the following deductions seemed plausible to Dr. Winkelman: Since the atrophy of the muscles was the only sign of a tumor in the anterior part of the superior parietal lobe, this may be considered as the trophic center. The proximity of this area to the motor and sensory cortex explains the frequent association of atrophy with astereognosis and hemiplegia by direct extension, posteriorly and anteriorly, in tumors of the parietal lobe. Whether the trophic influence in the cortex is localized purely in the designated area is difficult to state. However, we do know that in all of our operative cases of tumor of the brain, as well as in postmortem examinations of the parietal lobe in cases showing atrophy of the extremities, among other symptoms, this area was regularly involved.

Case 2.—This case illustrates the process of extension as already stated. Dr. Winkelman made a diagnosis of a tumor of the parietal lobe with the only localizable sign an atrophy in the left hand, a very slight degree of sensory disturbance, which could easily have been overlooked, and no motor signs. A marked increase in the atrophy later developed, with a stereognosis and complete hemiplegia on the left side.

Case 3.—The most remarkable and instructive case was that of a patient in whom atrophy of the muscles was seen to develop in a previously normal extremity, the first localizable sign in the course of a progressive lesion of the brain. The patient, a man aged 42, referred by Dr. D. Donnelly, had begun to experience jacksonian sensory and motor seizures localized to the left side of the face about three months before examination. When he was first examined, after having had two attacks, no neurologic signs other than a slight ironing out of the left lower part of the face with slight weakness were evident. The motor power was good. Dynamometer readings were: right hand, 90; left hand, 85. The reflexes were equal on the two sides. There was slight atrophy of the left hand, especially in the interosseous spaces. All tests for sensation gave negative results. Following the examination, the seizures became very frequent and seemed to be precipitated by certain positions and movements of the head. Roentgenograms of the skull gave negative results. The spinal fluid was under a pressure of 12 mm. of mercury. The Wassermann reactions of the blood and spinal fluid were negative. On Jan. 20, 1931, the jacksonian sensory attacks also involved the thumb and index finger, and later spread to the other fingers of the hand. On January 23, it was noted that the left upper limb was markedly atrophied. The hand was pale, the muscles soft and the overlying skin smooth and glossy. On February 17, the patient began for the first time to show slight evidence of sensory disturbances as to degrees of position of the fingers, but no astereognosis. On February 23, marked weakness of the left upper extremity and right-sided headache developed, and, according to reports from his physician, left hemiparesis with sensory disturbances had developed since then. In this case the lesion was localized in the postcentral area, extending over the Broca's region and growing upward into the parietal lobe. This patient also showed the susceptibility of the trophic influence in the cortex to pathologic processes. The patient was operated on on March 6, and the diagnosis was verified.

Other observers have found atrophy of the muscles in cases of disease of the parietal lobe. Von Monakow described, among the symptoms of lesions of the parietal lobe, unilateral muscular atrophy. Henry Head described a patient who was wounded in the right parietal region, with no resulting paralysis of the extremities except that the grip of the left hand was less than the right. He stated that the left forearm and hand were distinctly wasted and this was most visible in the interosseous muscles. There were associated with this marked incoordination and sensory disorders. Head also described graphically the type of atrophy that seems to be characteristic of lesions of the parietal lobe. He stated that the feature of the case was the hypotonic condition of the left hand associated with a peculiar change in its contours and general appearance. There was no gross wasting, but the differences between the two hands were profound. The left hand resembled that of a woman and was soft. The interosseal spaces were not wasted. They seemed, however, to be occupied by smaller and softer muscles. The grip of the right hand was firm and well sustained, but that of the left hand was like the impression received from the hand of a woman. The pressure was orderly, but gentle and harmless.

Time does not permit discussion of the literature on this subject. A number of authors—Quincke in 1888 and Petrina among others—have spoken of a trophic center located in the region of the motor cortex, corroborating the physiologic experiments on animals by Eulenberg and Lepine and also supported clinically by Rossolimo and Oppenheim.

Most of the cases in the literature on hemiplegic atrophy, whether due to tumor or other pathologic processes, have been associated with sensory changes. Weisenburg, in a study of 160 cases of hemiplegia at the Philadelphia General Hospital, also made the same observation. From these observations, one must admit that the trophic center is in the region of the somesthetic area.

Since 1888, against great opposition, Mills has insisted on the separate localization of the sensory cortex, and Grünbaum and Sherrington, in their classic experiments on anthropoid apes, proved that the motor areas occupied the precentral convolution and did not extend over to the postcentral region. These regions were also differentiated by Campbell and other anatomists by their characteristic histologic variations. Thus, in considering our cases from these known scientific observations, I believe that we are justified in locating the trophic cortical center in the parietal lobe.

DISCUSSION

Dr. T. Fay: I wish to say only that the lesion was subcortical and extended deep down toward the thalamus. The cyst was probably 3 cm. in diameter and approached the internal capsule, so that the subsequent reaction and edema noted on the fourth day might have been due to trauma near the internal capsule. A complete return of function indicates that this was a transitory factor and, therefore, probably edema. After removal of the cyst there was a defect in the substance of the brain about the size of a golf ball. These defects usually fill with fluid, but as the postoperative picture was not marked by stupor it is probable that the edema was localized.

I believe that Dr. Silverstein's points are well taken. At the Jewish Hospital I have recently had a case of a similar type. The atrophy was so profound that a diagnosis of infantile paralysis had been formerly considered. A lesion at the parietal lobe was found. According to Henry Head, the atrophy such as that Dr. Silverstein has described, which occurs in lesions of the parietal lobe and probably has a basis on the sensory disturbances is a matter for a great deal of discussion and study. Dr. Silverstein has called attention to a sign that may have great significance in lesions of the parietal lobe.

Dr. W. G. Spiller: In the child presented by Dr. Silverstein, the unilateral convulsions in the side opposite to the lesion of the parietal lobe began at the age of 2 years but soon ceased and reappeared about eight years later. It is stated that symptoms of the parietal lobe were absent. Possibly this may be explained by the early age of the child when the symptoms first developed. It is recognized

that in a right-handed child a lesion of the left cerebral speech area in the first years of age seldom causes persisting aphasia, because at this formative period of life the right cerebral hemisphere is capable of developing a speech cortex. In the child presented by Dr. Silverstein, a similar explanation may be employed for the absence of symptoms indicating involvement of the parietal lobe.

One may ask whether the smallness of the limbs on the side opposite from the cerebral lesion is to be considered as arrested development or atrophy. This makes little difference in the present case as the question at issue is the relation of the deficient size of the limbs to the lesion of the parietal lobe. A recent study by Kiss from Schaffer's clinic supports an old view of cerebral atrophy, namely, that the lesion of the pyramidal tract lessens or abolishes the stimulating impulses from the cerebral cortex which exert a biochemical influence on peripheral neurons. It is not difficult to believe that a lesion of afferent fibers to or in the parietal lobe may affect the trophic function of the limbs, possibly reflexly through the motor cortex, but as yet I cannot consider as proved that a lesion of the motor cortex has no relation to cerebral atrophy.

DR. A. SILVERSTEIN: In answer to Dr. Spiller as to the question of an arrest of development rather than an atrophy in the first patient presented in my report, I feel that in this case the atrophy was of a comparatively recent origin as manifested by the vasomotor changes in the overlying skin, the increase in the wasting of the muscles involved following the operation, and its great resemblance to other cases of lesions of the parietal lobe. Dr. Spiller stated that although he must admit that the parietal lobe may produce atrophy in the muscles of the opposite extremities, he is not convinced that the motor cortex cannot also produce this change. I may state that from careful studies of cases of hemiplegia without sensory disturbances, excluding those of long duration, there was little evidence of atrophy in the involved muscles. On the neurologic service of Dr. Winkelman, a few months ago, we had occasion to study two patients. One was a colored man with marked hemiplegic atrophy of a few months' duration, from whom there were removed two tuberculomas in the left parietal area. In contrast to this case, the second patient, also a colored man, with posttraumatic hemiplegia without sensory disturbances, of three years' duration, gave no evidence of peripheral wasting. There have been numerous theories to explain hemiplegic atrophy. The most recent report of Kiss, who accepted Schaffer's theory based on the Charcot dictum that alterations in the anterior horn cells in the spinal cord are responsible for the atrophy, failed to explain this condition because many cases in the literature do not show these changes in the cells and the latter have been seen without the presence of atrophy in the muscles. In all our cases, and most of those reported in the literature, of hemiplegic atrophy there were associated sensory disturbances. This means that the somesthetic cortex was involved, and in consideration of the latter, plus the presentation of cases without signs of involvement of the pyramidal tract, it is indeed likely that the parietal lobe is responsible for this atrophy.

MEDULLO-EPITHELIOMA OF THE BRAIN WITH METASTASIS TO THE HEAD, NECK AND THORAX: REPORT OF A CASE. DR. TEMPLE FAY.

This case is presented because of the comparative infrequency of the type of tumor, the rapidity of growth and early metastasis, the unusual size of the enucleated cerebral mass and the final termination complicated by metastasis to the head, neck, lungs and thorax.

History.—Miss J. deS., aged 16, an Italian, was referred to Dr. A. H. O'Neal, of Wayne, to the neurosurgical service of Temple University Hospital on April 13, 1930, and discharged on June 1. Her chief complaints were: a bulging mass over the right side of the head in the area of a former extensive decompression, nodular masses of the scalp in the craniotomy scar, with firm attachment to the bone and underlying structures, a nodular mass behind the right mastoid, severe headaches and progressive paralysis of the face, arm and leg.

The patient had been operated on in an adjacent neurosurgical clinic five months previously (Dec. 19, 1929). A right parietotemporal exploration had been made with removal of the bone flap to permit decompression. A tumor had been encountered and removed by electrocautery. The bulging began in the decompression area from three to four weeks after the operation. One month prior to admission, the patient lost the use of the left arm and leg. The mental state was not impaired. There had been no vomiting. Paralysis on the left was not complete in the leg, and the patient was able to walk with a cane at the time of admission.

Eleven months previously, the first symptoms began, with headache in the right frontotemporal region, in the mornings. Nine months previously, the headaches became worse; projectile vomiting ensued, and gradual paralysis of the left side of the body followed. Five months previously, the patient became stuporous and aphasic, with complete sensory and motor loss on the left side. Following exploration and decompression, a rapid and complete recovery followed. The patient was able to walk and to use the left hand, and headache and vomiting disappeared. She was comparatively well for three months when, with rapid increase of the growth in the area of decompression, symptoms again recurred, with headache but no vomiting and a rapid hemiparesis on the left. Five months after the former operation, she was admitted to Temple University Hospital.

Neurologic Examination.—In April, 1930, the patient was poorly nourished and had hemiplegia on the left side. She dragged the left foot in walking, and walked with the assistance of two people. Swaying and weakness were present. There was a large mass over the right temporal region, about the size of a grapefruit, which was definitely circumscribed with nodular spots in the center and periphery. The mass was tender to palpation, tense and semisoft. It did not transmit light and did not expand, pulsate or show changes on coughing or respiration.

The pupils were round, regular and equal. They reacted to light and in accommodation. The ocular movements were full. There was weakness of the left leg and left palpebral fissure, and weakness of the left side of the face, including the forehead. Very little movement remained in the left upper extremity. There was marked weakness in the left lower extremity. The reflexes were increased on the left; a Babinski sign and clonus were present on the left. Touch, pain and sense of position were impaired on the left. Vibratory sense was normal. The left abdominal reflexes were absent. Stereognosis was lost.

Eye Examination.—On April 14, the right media were clear; the disk showed papilledema of 3 diopters, and vision was 20/30. On the left, vision was 20/200; the media were clear, and the disk showed from 3 to 4 diopters of swelling.

Exploratory Operation and Course.—On April 15, under local anesthesia, I made a small incision in the center over the large bulging mass in the right temporoparietal area. On palpation the mass seemed cystic. The skin was opened, as well as the dura and the cortex. Exploration was carried down to a depth of 3 cm., when, with the failure to encounter fluid by direct inspection or by needle, it was evident that a large mass existed and was defined as being separable from the mass of the brain. With the fingers it was possible to discern the extent of the tumor and a rapid opening was made, requiring section through the adherent dura and the cortex. A huge tumor was encountered, which extended from the occipital lobe to the precental area and to a depth of 6 cm., lying against the ventricular wall and including almost the entire temporal lobe. The mass was as large as a grapefruit; it was one of the largest tumors I have ever seen; it was rapidly dissected free from the tissue of the brain, with combined spatula and finger dissection; it was adherent to the middle cerebral artery, which was carefully protected, and the branches were severed; bleeding points were controlled by coagulation. With the electric cautery the mass was delivered within a few minutes; the cavity remaining was extensive. The general condition of the patient was not good. At the beginning of the operation she was given 50 cc. of a 50 per cent solution of dextrose, with 150 cc. of physiologic solution of sodium

chloride. Shortly after the removal of the tumor, the pulse and blood pressure were not obtainable. The head of the table was lowered and an additional 35 cc. of dextrose and, shortly after, 300 cc. of citrated blood were given. Remaining tumor attachments in the cavity were severed by the electrocautery. The bed of the tumor mass was drained with a cigaret drain. The skin was closed with a double layer of silk. The operation lasted two hours.

The patient was returned to the ward in a poor condition. The pulse was hardly perceptible, its rate being 180, and the blood pressure was 30 systolic and 0 diastolic; the respiratory rate was 28. Hot enemas were given, and a continuous proctoclysis, a solution of pituitary, atropine, strychnine and digalen-Roche (Cloetta) were given. There was gradual improvement in the general condition, and within two hours the patient was apparently none the worse for the operation. During the following twelve hours she improved, and twenty-four hours after the operation the blood pressure was 108 systolic and 80 diastolic; the pulse rate, 120; the respiratory rate, 20 and the temperature, 98 F. She was conscious, talking and in good spirits. She could move the face and arm on the left side, including the fingers.

Removal of Nodular Mass.—On May 21, under local anesthesia, I made an incision, about 6 inches (15.24 cm.) in length, along the anterior part of the frontoparietal region and exactly in line with the scar of the initial operation. The scalp was reflected; bleeding was checked. The dura was separated, as it had not been closed at the first operation. A tumor about the size of a hen's egg was removed from the anterior margin of the operative field. It was easily dissected from the cerebral substance, though it was difficult to tell whether or not some of the margins of the tumor were not attached to bone. However, the skin, bone and dura was not infiltrated to any extent. The cortical wall at this point was extremely thin, and the ventricle on this side was greatly dilated; during the procedure it was broken through and about 2 ounces (59.2 cc.) of cerebrospinal fluid drained away. The edges of the tumor were cauterized with the electric needle. No effort was made to define the dural edges as they had become retracted and adherent. The edges of the skin were then tier-sutured with silk. A small nodule just behind the left ear, right over the mastoid process and invading the origin of the sternocleidomastoid muscle, was removed. The tissue of the tumor was similar in appearance to that removed from the brain. The incision was sutured with two silk sutures. The patient was returned to the ward in a good condition.

Neuropathologic Examination.—Dr. N. W. Winkelman reported that a section showed a neoplasm with a fairly uniform make-up. The arrangement was either in sheets, folded in place, or there was a concentric arrangement around a central vessel or space. Much degenerated tissue was present in small islands between these cellular areas. The make-up consisted of epithelial-like cells, which were certainly glial in origin, with oval nuclei containing scanty chromatin and with well defined cytoplasm. No blepharoplasten were seen with appropriate stains.

There was here a primitive attempt to mimic the embryonic nervous development with each concentric arrangement of cells.

Glioma of the medullo-epithelioma type was diagnosed from the microscopic observations.

Further Progress.—The patient made a prompt recovery from the two operations. Frequent tapping of cerebrospinal fluid in the area of the former nodulation was required for two weeks following the operation. A biopsy of the enlarged mass behind the right mastoid showed a medullo-epithelioma metastatic to the posterior cervical lymph chain. A roentgenogram of the chest taken on May 21 was clear.

The patient was discharged on June 1. She was able to walk, to use the left hand comparatively well and had complete return of power in the left side of the face.

The nodular masses in the original incision of the scalp enlarged to the size of a duck egg in spite of intensive, deep, irradiation given by Dr. Pancoast and Dr. Pendegrass. Irradiation was abandoned as ineffectual at the end of the third month. About thirty individual tumors appeared in the next three months. The glands of the neck became swollen on the right side, the nodular masses appearing under the clavicle.

Five months after discharge from the hospital, the patient died with signs of massive consolidation in the lung. At the time of death, her appearance was grotesque. The many large tumors originating in the first incision had reached the size of lemons and extended in bulging masses down the neck. The distortion of the scalp and head from these metastatic lesions made the patient almost unrecognizable. In the central portion of the decompression, where the large cerebral mass had been removed, there was no evidence of a return of the primary lesion. An autopsy was not permitted. Death occurred ten months after the original operation, five months after the second enucleation and one year and two months after the initial onset of symptoms.

Comment.—The case is of interest in that: a medullo-epithelioma is comparatively rare at the age of 16; the rapid tendency to metastasize and the failure to respond in the slightest degree to extensive, deep irradiation, as well as the direction of metastatic extension; the size of the enucleated tumor; the mechanism of the multiple transplantations of tumor cells into the original incision is unexplainable as removal of the original mass had been undertaken by electrocautery.

DISCUSSION

DR. J. H. LLOYD: Could this metastatic tumor have arisen from a hypernephroma? At Blockley, I saw a child who had such a growth just behind the orbit. It was very malignant and of very rapid growth. Autopsy showed another similar tumor in the parietal region of the brain which was beginning to perforate the skull. In his work on internal medicine Dr. James C. Wilson has given a picture in a similar case, and almost like this one of Dr. Fay, as a growth from a hypernephroma. The primary growth in or about the kidney is, as I understand, composed of embryonal cells and is highly malignant, throwing off metastases which are apt to be located in the brain. These cases are likely to occur in early life.

DR. T. FAY: I think that the possibility of a hypernephroma is of interest. Such lesions have occurred within the brain. This is, however, of a distinctly neuroblastic type. The tumor appears in rosettes and resembles the early formation of the neural tube. It is one of the most malignant and active types of tumors within the brain. It metastasizes rapidly. A hypernephroma may be rapidly malignant, but the characteristics are distinguishable. Perhaps Dr. Alpers can differentiate the fundamental differences of staining and other characteristics between the two.

CEREBELLAR ATROPHY: TWO CASES WITH MOVING PICTURES AND PATHOLOGIC SPECIMENS. Presented by DR. WALTER FREEMAN.

Two patients with degenerative conditions affecting the cerebellum have recently come under observation, and a permanent record of their motor disability has been obtained by means of moving pictures. In the first case the peculiar movements were so marked that the patient was believed to have dystonia, but there was no doubt of the cerebellar involvement in the second case.

CASE 1.—*Cerebellar heredo-ataxia of Pierre Marie.*

A white man, was admitted to St. Elizabeth's Hospital on Dec. 27, 1927, at the age of 39, and died in May, 1930, of lobar pneumonia. As a child he had been sickly and backward. At 12, he had some acute illness for which intraspinal serotherapy was instituted. Following this there was progressive disability, with emaciation, scoliosis, irregular movements and finally loss of the power of articulation. He seemed to understand and to endeavor to cooperate, but was always

hampered by coarse, irregular, involuntary movements. There were marked hyperextensibility of the joints, muscular atrophy and loss of reflexes. There was no nystagmus, and no corneal ring. Repeated attacks of pneumonia in the lung compressed by scoliosis were noted before the final illness.

Necropsy disclosed marked atrophy and firmness of the cerebellum. The basal ganglia were normal; the pons was well preserved. The olivary bodies were atrophic. Sections revealed intense gliosis of the cerebellar cortex and white matter, with loss of Purkinje cells. There was well marked gliosis with disappearance of myelin sheaths in the dorsal columns of the spinal cord. One brother has had similar motor disturbances.

CASE 2.—*Senile atrophy of the Purkinje cells in the hemispheres.*

A colored man was admitted to St. Elizabeth's Hospital in September, 1896, at the age of 60, and died in August, 1930, aged 94. The diagnosis made on admission was chronic melancholia. Ten years later, the record indicates that he was confused, imperfectly oriented and forgetful, that he entertained a number of bizarre delusions and had no insight. He worked well on the ward until 1918, when he began to be unsteady on his feet; after 1920, he had to be assisted in walking. Coordination gradually grew worse until it became necessary to spoon-feed him and to keep him in bed. While in bed or sitting in a chair, he presented no involuntary movements, but any voluntary effort brought forth gross tremors with past pointing, asynergia and adiadokokinesis. Nystagmus was absent and he could stand unsupported, even with the eyes closed. Congestive myocardial failure caused his death.

Necropsy disclosed thrombosis of the pulmonary artery with other indications of cardiac failure. The brain weighed 1,191 Gm. and was not unduly atrophic. The cerebellum was proportionately small but of normal color and consistency. Microscopically, there was almost complete disappearance of the Purkinje cells in the hemispheres, although they were preserved in the vermis. There was no significant gliosis. In some places, remnants of basket fibers could be seen without Purkinje cells. The other structures of the brain were approximately normal for a man of this age.

A CASE OF GLIOMATOUS CYST OF THE SPINAL CORD IN A BOY SIXTEEN YEARS OF AGE. Presented by DR. A. M. ORNSTEEN.

The family history in this case is without significance and the past medical history is not unusual except for the fact that from 11 to 14 years of age the patient suffered from gastro-intestinal symptoms in the form of attacks of nausea, vomiting and dull abdominal pain, which occurred most often in the mornings and were relieved after breakfast; they were accompanied by headache and constipation. For the two years prior to presentation he had been free from these symptoms.

The onset of the present condition had been noticed rather abruptly three years previously; while he was carrying a heavy box, both lower limbs felt abnormally weak. It appears that from this time on the condition slowly progressed. The legs have tired quickly on exertion, and it was noticed that the gait was awkward, causing him to stumble frequently. Several months after the onset, he experienced numbness in the tips of all the fingers, especially when he touched objects. There was also some awkwardness in the use of the hands, so that it was difficult for him to button his clothes unless he watched his fingers. For about a year this symptom has not been present and the use of the hands has been much improved. Another trauma or strain occurred last year while he was attempting to lift a log. Since then, the gait has become more uncertain, so that he cannot control the movements of the feet in walking. He fell about three months previously, he thinks that the weakness of the legs has been more pronounced since then.

About two and a half months ago, he noticed that while in the bath he was unable to appreciate the temperature of the water with the left foot and leg. He could not tell the difference between hot and cold water with that extremity. He

believed that the sensation was disturbed up to the hip. He pinched the skin of the affected part and did not feel pain. He had a crawling sensation on the bottom on the left foot, extending several inches above the ankle.

Station and gait were very ataxic, being on a wide base and with excessive elevation of the knees. When the patient sat on the edge of the bed with outstretched arms and eyes closed, the trunk swayed moderately, the right arm sank to a lower level and the fingers of the right hand were irregularly alined as compared with those of the left, suggesting greater disturbance of tone on the right. The power in the upper limbs was approximately normal (dynamometer readings: right, 70; left, 65). The reflexes of the biceps were weak on both sides; the reflexes of both triceps were absent; there was no Hoffman's sign. The finger-to-nose test was well done on each side, as were tests for diadokokinesis. The Stewart-Holmes' arm sign was somewhat hyperactive on both sides, but more so on the right. The patient could arise from the supine to the sitting position with the arms folded across the chest. The kneejerks were greatly exaggerated, perhaps slightly more so on the right, with a greater pendulum swing on the right indicating greater disturbance of tone. Bilateral ankle clonus was present, as well as bilateral Babinski, Rossolimo and Mendel-Bechterew signs. The muscle tone in both lower limbs was normal and the motor power was well preserved. The abdominal and cremasteric reflexes were absent. Sense of vibration was lost at both ankles; it was slightly perceived on the shins, slightly more on the patellas and well on the iliac crests and wrists; it was lost on the spinous processes up to the sixth thoracic vertebra, being well recognized on the fifth. The sense of position in the toes was completely lost; it was preserved, however, at the ankles and was normal in the fingers. The sensations of pain and temperature were greatly impaired in the left lower limb and abdomen up to about the eighth thoracic segment; above this level it was moderately impaired as high as the seventh cervical segment. On the right, there was less impairment of pain and temperature of the trunk and upper limb, extending from the twelfth thoracic to the first thoracic segments. Touch sensibility was preserved throughout, but was not as readily recognized on either side of the body up to the midthoracic region; it was more disturbed on the left. There was a mild degree of pain and temperature disturbance on the left side of the neck and face. There was no sign of oculosympathetic involvement on either side, nor of abnormal secretory reactions. There was, however, a marked difference in the vasomotor reflexes below the fourth thoracic segment on both sides of the body. Above this area the vasomotor responses were with reddening of the points stroked, with rather exaggerated bordering reactions in the form of diffuse reddening for about ½ inch to either side. Below this level, especially in the lower limbs, the stroked area became white and remained so for a long time without reddening in the adjacent tissues. It was therefore possible to write on his skin in red above the fourth thoracic segment and in white below.

Roentgenograms of the spinal column were normal. On spinal puncture the initial pressure was found to be 4 mm. of mercury; on deep jugular compression it rose very slowly to 14 and fell to 8 mm. on release of pressure. Straining and coughing responses were also defective in that they were very weak and rose only to between 10 and 14. The fluid was clear and contained 5 lymphocytes, 1 polymorphonuclear lymphocyte and 9,700 red blood cells, and 2 units of protein; it gave a negative Wassermann reaction. The Wassermann reaction of the blood was negative. A roentgenogram of the skull showed hyperostosis of the frontal region, which was reported as probably having no clinical significance. Examinations of the blood and urine gave negative results.

Therefore, there was evidence of a lesion of the spinal cord involving both pyramidal tracts, both posterior columns, the right anterolateral column and the central gray matter throughout the thoracic cord, with extension on the left into the cervical areas. The syringomyelic picture was present by virtue of the central involvement, and by the involvement of the tract it was presumed that a tumor was also present. A glioma with a cyst was the pathologic condition I had in mind.

Book Reviews

THE CLIMACTERIC (THE CRITICAL AGE). By GREGORIO MARANON. Price, $6.50. Pp. 425. St. Louis: C. V. Mosby Company, 1929.

A subject that is engaging the attention of physicians generally and is enjoying the recognition of a real theme in the endocrine field is the menopause. Many books on general medicine, as well as on the special topic of endocrine disturbances, give but scant notice to this phase of man's life span. When one recognizes the facts that depend on the glandular disturbances of this condition, one is at once confronted with a widespread symptomatology that enters into every field of medicine, particularly, however, the nervous and mental states and the cardiovascular concomitants.

Gregorio Maranon, of Madrid, in the second edition of this work, translated from the Spanish by K. S. Stevens, gives a real monograph on this complex condition. His point of view is broad and undoubtedly correct, in that he considers the insufficiency and involution of the genital glands as only one factor of a widespread disturbance. His thesis, which he demonstrates in succeeding pages is: "The pathogenic mechanism of climacteric symptomatology is not limited to insufficiency of the genital gland, as has been held, but it is rather the expression of a complex endocrine crisis which varies in different individuals. In this crisis the outstanding feature is gonadal insufficiency to be sure, but other glandular disturbances occur coincidently and form an essential part of the crisis. Our knowledge concerning some of these various glandular disturbances is now fairly well established."

And so, for about seventy-five pages his demonstration continues, showing the part played by the ovarian factor, the thyroid, the suprarenal glands, hypophyseal factors and the vegetative nervous system in the picture-complex of the climacteric. Then follow chapters on the various disturbances, chiefly in the psychic domain. One of these chapters is on the "The Critical Age in the Male." His attitude is one at which many would cavil; while some writers, notably Krafft-Ebing and Vinay, deny the existence of such an involutional state in the male, Maranon "boldly asserts" its existence, but at the same time treats it on a much lower and less important level than he does the female state. While this is undoubtedly a proper view in the opinion of the reviewer, yet Maranon's statement of the case from the psychiatric angle can hardly be accepted. It is that the symptom known to him as "sexual melancholy" is of little importance in the male. The reason for this, says Maranon, is that the extinction of the genital function in man is of less concern to him than her loss is to woman, and that states of "sexual melancholy" are very rare in the normal man undergoing the climacteric. In clinical experience the mere thought of the possibility of sexual impotence can bring about the most profound change in man's personality and behavior, and clinics are filled with this type of case. But Maranon's views on many of the problems attendant on the climacteric are refreshingly naive and interesting, entirely apart from his understanding of the endocrine and general medical problems underlying the entire situation, and will repay many hours of reading his volume. His pluriglandular theories and their application are more than well balanced, and to read his work will give a mine of information in this field.

DIE UMERZIEHUNG: DIE HEILPÄDAGOGISCHE BEHANDLUNG SCHWERERZIEHBARER, ENTGELEISTER UND STOTTERNDER KINDER UND JUGENDLICHER. By KARL CORNELIUS ROTHE. Price, 4.90 marks. Pp. 168. Halle, Germany: Carl Marhold, 1929.

The notion of reeducation supplants the notion of after-education. The former seeks to change the whole person, the whole personality. Education may be

defined as the determination of the future activity of the patient by the present activity of the teacher. The teacher provides both the motives and the inhibitions. Education has a second task. It should tear down the undesirable to replace it with the new and better. Reeducation is the making over of the patient according to a consciously conceived plan. The individual person brings into the world a definite constitution that provides the building material from which the personality is developed in the environment in which he lives.

The author emphasizes the need of cooperation between the physician (psychiatrist, neurologist) and the teacher. In working with the former, the latter acquires a better picture of the whole person. In the investigation of the patient, refined and expensive apparatus such as is found in hospitals and clinics may be used if the teacher is cooperating with the physician. Considerable emphasis is placed on physical measurements as the basis for the determination of physical types which are thought to be important. Such physical types as asthenic, leptosome, muscular and pyknic, and such racial types as Nordic, Mediterranean, Alpine, Dinaric and East Baltic are listed and discussed.

In regard to sexuality, the author holds that the reeducator is not justified in prying into the sexual life of the patient. The first virtue the reeducator must acquire is a tactful respect for the personality entrusted to him. Both the teacher and the physician should assist in the sex education of the patient. Reeducation should be broken up into partial goals which lead to the main goal. Partial goals may consist of self-control, cleanliness, a pleasant cooperative attitude and freedom from bodily ailments (nasal and pharyngeal catarrh, tonsillitis, etc.). In the main there are two forms of reeducation. One is the strenuous, vigorous type in which the teacher energetically and quickly attacks the bad habits of the child and establishes new habits. The child is required to "snap out" of his ways of doing things. The other type consists of a slow, long, patient reeducation of the child. Individual differences determine the form of method to be used. With either form the teacher must always be truthful and honest with his pupils. He must gain their love and confidence. In the realization of this goal, the teacher's personality is of prime importance. The majority of handicapped children have wounded hearts. A study of the situations out of which the child has come is indispensable to a good understanding of his case. The reeducation of the child begins with the reeducation of its parents. It is a splendid practice to have the children read autobiographies and biographies of those who have succeeded despite certain physical and mental handicaps. Children should be taken out of their own inner worlds. Games, plays, gardening, carpentry and outdoor sports are valuable in this connection. Success in the treatment of children is dependent to a large measure on their ages. The younger the child the more apt is the improvement to be rapid and permanent. Therapy and school instruction are combined in such a way as to permit the defective child to live a relatively normal life with normal children.

A Dictionary of Terms Dealing with Disorders of Speech. By Samuel D. Robbins, A.M., and Sara M. Stinchfield, Ph.D. Price, 65 cents. Pp. 28. American Society for the Study of Disorders of Speech, 1931.

The student of disorders of speech is constantly running across terms in the literature with which he is not familiar. In many cases each author uses his own terms; in some cases as many as twenty terms have been given to one and the same disorder. Realizing the need of a systematic international classification of disorders of speech, the American Society for the Study of Disorders of Speech appointed a Nomenclature Committee to prepare such a classification. The committee has authorized the publication of a tentative dictionary at this time for the express purpose of giving those engaged in correcting disorders of speech an opportunity to criticize and improve its definitions.

The committee has tentatively divided disorders of speech into seven classes: dysarthria, dyslalia, dyslogia, dysphasia, dysphemia, dysphonia and dysrhythmia.

Each class, in turn, has been divided into descriptive groups by replacing the prefix dys with a suitable descriptive prefix. Each group, in turn, has been further divided into causal varieties by adding to the name of a given group suitable causal suffixes. There follows a tentative condensed classification which illustrates how this principle works out, of which the fourth and fifth groups are of especial interest to neurologists:

IV. Dysphasia

Impairment of the power of language, due to weakened mental imagery:

A. Agraphia.
B. Alexia—Word-Blindness.
C. Articulatory Aphasia.
D. Auditory Aphasia—Word Deafness, etc.
E. Mixed Aphasia.
  1. Agrammaphasia—Syntactical Aphasia—Word-Salad Speech.
  2. Aphasia—Speechlessness.
  3. Bradyphasia—Groping Speech.
  4. Cataphasia—Repetitious Speech.
  5. Paraphasia—Word Substitution.
F. Total Aphasia.

V. Dysphemia

Variable nervous disorders of speech due to psychoneuroses:

A. Aphemia—Dumbness.
  a. aphemia hysterica—hysterical mutism.
  b. aphemia pathematica, due to fright or passion.
  c. aphemia plastica—voluntary muteness.
  d. aphemia spasmodica—spasmodic dumbness.
B. Paraphemia—Neurotic Lisping.
C. Spasmophemia—Stuttering—Stammering.
D. Tachyphemia—Nervous, Rapid Speech.

It is obvious that other classifications might be made, and the difficulty of combining several points of view has not been satisfactorily overcome; but the classification is tentative and the authors are asking for advice. For example, many would not look on spasmophemia (stuttering) as due to psychoneurosis.

There follow twenty pages of dictionary which is good as a preliminary, but needs a meticulous editing by a trained neurologist.

Fifteen per cent discount is allowed on orders of fifteen or more up to fifty; 25 per cent is allowed on fifty or more copies of the book.

No Need to Stammer. By J. St. John Rumsey. Price, $1.25. Pp. 75. London: Methuen & Company, Ltd., 1923.

In the introduction to this book, Dr. Halls Dally briefly states the main problem: "Speech constitutes the chief vent for the emotions. Under ordinary conditions its function is automatic, but the mechanisms concerned in it are so delicate that very slight disturbance of them is sufficient to upset the balance, and so to impair or destroy the whole beauty and precision of the process of utterance. In the case of stammering it becomes necessary to go deeply into the reasons which lead to such disturbances, when it is nearly always found that a deep-seated sense of fear is present as the underlying causal factor. The fear sense disorganizes speech processes, and although, as every sufferer is aware, certain conditions may augment or lessen this dread, nevertheless the basis of the malady is primarily psychical and only secondarily physical." He adds that the "speech center" has been rendered sensitive by heredity or illness and therefore bears the brunt of the psychic disturbance.

With such a good start, it is suprising to find that the rest of the book is devoted to training the speech, voice and respiration. Some good points are brought out, such as the fact that delayed vocal mechanism is the chief speech difficulty,

and that the patient should put his mind on pronouncing the vowel; but that this "delayed vocal mechanism" is the "most frequent cause of stammering" is not at all in agreement with the admirable statement of etiology in the introduction.

Much attention is paid to articulation, and many exercises and rules are given; for example, in summary, there are the following rules: Breathe deeply, expanding the chest in all three diameters, and using the steady compression described. Keep the larynx down and the throat open and loose. Open the mouth freely in speaking, to let the sound come out. Keep the tongue as flat in the mouth as is possible for correct production of vowels and consonants. Keep the jaw forward, so that it drops toward the toes. Speak slowly to enable the vocal mechanism to do its work properly. Always speak on a low note. It is the correct way to use the vocal mechanism. It adds dignity and weight to what is being said, and is therefore of great importance in all kinds of professional work. It helps every stammerer. In some cases it is all the help needed to gain fluency of speech.

From the point of view of the stammerer it would seem that the admonition as to pitch was the only helpful rule.

The author, however, states that even after a stammerer has been taught the correct method and "it only remains for him to use consciously the new method," "curiously enough" it is in this last that failure may occur.

Such hybrid books on treatment show a lack of courage on the part of the medical profession to leave outworn methods that have been proved useless. If the "basis of the malady is primarily psychical," instructing the patient to think of the position of his tongue in his mouth, "to breathe deeply, expanding the chest in all three dimensions," etc., can do no good and probably can do harm by confusing the issue.

MENTAL ASPECTS OF STAMMERING. By C. S. BLUEMEL. Price, $2.50. Pp. 152. Baltimore: Williams & Wilkins Company, 1930.

This book was written primarily for use in the schoolroom, with the youthful reader in mind. It deals largely with therapy, but describes the causes and manifestations of stammering in the first chapter. Stammering is looked on as an impediment of thought, and is said not to arise from physical causes. As evidence the author shows how capricious the symptom is and how a stammerer may avoid "difficult" words and thus entirely conceal the impediment from his audience, although he knows perfectly well he is struggling with an impediment of thought. Other impediments—in swallowing, breathing, walking and playing instruments—are then described as illustrative examples to show the lay reader what a functional nervous disturbance may be. Cases are briefly cited.

According to the author's theory, the stammerer's difficulty is occasioned by a momentary "amnesia" or loss of memory for the word he wishes to speak. His memory for word-sounds is weak, just as one's musical memory may be weak; thus the word-sound fails at times to emerge in the mind. If the speaker attempts to proceed with his unaided motor images of speech, stammering results. Amnesia occurs, not because the stammerer waits on his memory, but because he is confronted with a break in the continuity of consciousness.

Part II takes up thought training as the basis of speech corrections. The remedy for stammering consists in thought training rather than speech training. This is necessarily so, since stammering is a thought disturbance and not a speech defect. In the corrective training, thoughts are disciplined by drilling them like soldiers; they are brought first into line, then into step and finally into orderly maneuver. Through this drill the stammerer learns to focus his attention more sharply on the mental process of speech, thereby avoiding recoil of imagery and incoordination of thought. The chapters describe how exercises are carried out for kindergarten children, grade school children and adults. Many of these exercises seem good and have stood the test of time. The author specifically states that they have no therapeutic value other than furnishing artificial occasions for speech, for the student improves by learning how to think, not how to talk. With early cases of stammering, treatment should consist only of rest in bed and the use of

sedatives, e. g., enough phenobarbital to keep the patient drowsy. He should not have visitors, and should be given little chance to talk. The parents are urged to understand the child's difficulties, but the accent seems to be on speech difficulties, not emotional difficulties.

On the whole, the book is a distinct advance over the usual manuals of speech training. The physician's energy is directed to training the mind, not the speech. But the mind is rather too simply schematized, and practically nothing is said of the importance of relieving the child of emotional stress by a thorough understanding of his problems, and by education of the parents as to how to relieve this stress. The plan is excellent for schools and classes, but is not adequate for individual private patients with cooperative families.

BECAUSE I STUTTER. By WENDELL JOHNSON. Price, $1.50. Pp. 127. New York: D. Appleton & Company, 1930.

This is a rather disappointing book. Starting out with "my purpose is to make an admission, a confession, a bald statement of subjective fact," the author gives an interesting account of his early life, but then under "Facts in General" he theorizes and gives his rather immature ideas as to etiology. For example, "stuttering, if my self-analysis is to be relied upon, is not a neurosis; a neurosis may, however, develop out of the fact that a glib society places a severe burden on the stuttering individual." And on the next page he makes the not easily reconcilable statement, "the occurrence of stuttering is determined not so much by the particular sounds or sound combinations met with in a particular location in a sentence, but more by the social situation in which speech is attempted."

Chapters III to IX give a story of the author's youthful development, but the reader would like to have more specific data concerning family relations. The continuity is interrupted by theorizing, often boring in its redundancy. The last chapter, "Stuttering in Detail," gives a good subjective picture of what it feels like to stutter.

The book would have been better if it had been written either by a more naive or by a more maturely educated person. For those who have dealt with few stutterers or for teachers or parents who want to know some of the feelings of a stutterer, the book has value.

PSYCHOLOGICAL FACTORS IN THE PASTORAL TREATMENT OF SCRUPLES. By J. J. MULLEN. Studies in Psychology and Psychiatry. Volume 1, no. 2. Price, $1.25. Pp. 165. Baltimore: Williams & Wilkins Company, 1927.

The author presents his objections to the theories held by Freud, Janet and others with regard to obsessions and scruples. He disagrees with Freud on the pansexual etiology and with Janet in his emphasis on dissociated consciousness in obsessions. The interest in this paper is not so much in the very severe cases as in the less abnormal cases met in pastoral experience. A section of the paper describes a questionnaire study of scrupulosity, by which answers to questions about scruples and childhood fears were secured from 400 girls of high school age in a Catholic academy. The type of person studied and the suggestive nature of the questions are probably responsible for the large number of scruples reported. A further section of the paper includes studies of three cases of scrupulosity from religious history.

In conclusion, the author discusses methods of treatment. He finds the methods of psychoanalysis inadequate, and agrees with Janet and others that hypnotism and suggestion are of little value for the scrupulous patient. He does not agree with Janet as to the concept of psychic tension, and he thinks that Janet has little to offer from the point of view of practical treatment. He advises a method of rational persuasion or reeducation, which presupposes "reasonable analysis and as intimate as possible an understanding of the individual." Treatment along such lines would be carried out by the Catholic authorities with the cooperation, whenever necessary, of sympathetic medical advisers.

THE SYMBOLIC PROCESS AND ITS INTEGRATION IN CHILDREN. By JOHN F. MARKEY. The International Library of Psychology, Philosophy and Scientific Method. Pp. 192. New York: Harcourt, Brace & Company, 1928.

The purpose of this book is to disclose the origin and integration of the symbolic process. The author surveys the writings of American sociologists, evaluating their contribution to the solution of this problem. The method of analytic psychology is rejected as making an enigma of the symbolic process. Gestalt psychology is criticized as merely pointing out the mystery of thought without furnishing an explanation of its nature. Behaviorism, which the author holds the most fruitful of methods, is also criticized, since it ignores the influence of social factors in the development of thinking. The behaviorist method, when it does take into consideration the effect of social intercourse, can afford a satisfactory account of the origin of symbols and their integration.

An interesting reinterpretation is made of the experimental work done on the development of language in children. It is shown that language symbols have a behavior content and a social reference. By studying the first words used by children from a functional rather than from the customary grammatical point of view, Markey makes more clear both the behavior content of words and their origin in social activity.

He reveals the continuity between animal and human behavior in this connection by analyzing the experiments that have dealt with delayed reactions in children and animals. He relates the presymbolic type of behavior to the symbolic process through an intermediary stage and shows continuity from the simplest type of immediate response to reflective thinking. The account given of the origin of the symbolic process is ingenious and valuable, and the reason for its continuance because of its value for social control is made clear.

A theory of the origin of language which associates it with sex behavior is original. The author holds that the emotional excitement and cooperation characteristic of sex behavior provide conditions favorable to the production of language symbols. While this may be one source of symbolic language, evidence is not forthcoming to show that it precludes other sources that have been suggested, such as the group dance or song, which also furnish the conditions on which Markey lays stress.

The book is a valuable synthesis of work done in the fields of behaviorist psychology and the psychology of language, and should be stimulating to psychologists and sociologists alike.

LE DÉVELOPPEMENT MENTAL ET L'INTELLIGENCE. By HENRI PIERON. Price, 10 francs. Pp. 96. Paris: Félix Alcan, 1929.

This short book, based on four lectures given at Barcelona in 1926, is a survey of the important psychologic problems in the study of intelligence and the measurement of mental development. It is a very concise presentation, but is none the less comprehensive. The author tries to relate the theoretical aspects of the problem and the increasing body of fact gained from practical experience with psychologic tools.

The first lecture deals with the stages of mental development of the individual as a unified organism and as a part of the social group. The second lecture on the measurement of developmental levels gives a critical discussion of various mental tests, of the rate of mental growth and of the limit of growth. In the third and fourth lectures this discussion is carried further, and the importance of an analytic study of the individual's mental development is emphasized. The author points out that a simple average of abilities on various tests is sufficient only for gross classification, and that this average should not be confused with true intelligence, which he takes to be the ability to solve problems.

RACHITHERMOMÉTRIE HUMAINE: RECHERCHES THERMOÉLECTRIQUES. By PAUL SCHIFF. Price, 20 francs. Pp. 107. Paris: Louis Arnette, 1927.

By means of a thermocouple inserted through the lumbar puncture needle, the temperature of the cerebrospinal fluid was measured in eighty instances (seventy-two patients) and compared with the rectal temperature.

In fifty instances in which the rectal temperature was normal (between 36.8 and 37.3 C. [98.2 and 99.1 F.] with an average of 37.15 C [98.8 F.]), the temperature of the cerebrospinal fluid averaged 37.68 (99.8 F.) or 0.53 C. higher than the rectal temperature. In forty-seven of the total of eighty-one examinations, the temperature of the cerebrospinal fluid was 0.5 C. or more higher than the rectal temperature, the greatest difference being 1.5 C. in one instance, while in only two instances was the temperature of the cerebrospinal fluid more than 0.2 C. less than the rectal temperature, the greatest difference being 0.7 C. in one instance.

THE MEANING OF PSYCHOANALYSIS. By MARTIN W. PECK, M.D. Price, $2.50. Pp. 273. New York: Alfred A. Knopf, 1931.

There have been many large and small books on psychoanalysis; this one of only 273 pages is one of the most compact, and yet it is so written that the average student, for whom it is intended, can obtain an idea of the main structure of the theory of psychoanalysis and its application and treatment, providing he has had some prior knowledge of the subject. The publication of this book is an outgrowth of a brief course of lectures on psychoanalysis given by the author as part of an elective course in psychiatry at the Harvard Medical School. The theory of psychoanalysis and its treatment is exposed in 160 pages. The balance of the book is made up of illustrative cases. At the end there is a glossary of the words used in psychoanalysis. Obviously, this book is only for students.

UEBER PSYCHOANALYSE. By SIGMUND FREUD. Eighth edition. Price, 2 marks. Pp. 62. Vienna: Franz Deuticke, 1930.

Under this title is reprinted for the eighth time the five lectures delivered by Freud at the twentieth anniversary of Clarke University, in Worcester, in September, 1909. Freud's visit to America at that time has become a landmark in the history of psychoanalysis, and in reading over these lectures delivered twenty years ago one is struck not only by their lucidity but by the fact that the fundamentals there presented remain today the essential working principles of psychoanalytic therapy.

EXPERIMENTS WITH HANDWRITING. By ROBERT SAUDEK. Price, $5. Pp. 394. New York: William Morrow & Company, 1929.

From the author's point of view handwriting is an indication of many things. The reviewer does not take much stock in it. However, if one wishes to believe that handwriting is an indication of character, this book is as good as any.